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OBJECTIVE TESTING OF MARIJUANA-INDUCED VISION CHANGES

Arthur Jampolsky, et al

Optical Sciences Group

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Final Report

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April 30, 1973

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Visual Sciences Division
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OBJECTIVE TESTING OF MARIJUANA-INDUCED VISION CHANGES

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FOREWORD

This Final Annual Report was written for the U.S. Army Medical Research and Development Command by the Investigators of a one-year study that was supported by a U.S. Army Basic Contract (No. DADA17-72-C-2083) awarded to the Visual Sciences Division of the Optical Sciences Group, San Rafael, California, which directed, guided, and administered the research study. The experimental phases of the study were conducted primarily at the Smith-Kettlewell Institute of Visual Sciences of the Pacific Medical Center in San Francisco and secondarily at the Langley Porter Neuropsychiatric Institute of the University of California Medical Center in San Francisco. Some of the data analysis was performed at the School of Optometry, University of California, Berkeley.

We recognize with appreciation the dedicated service of our laboratory technician and electronics engineer, Michael Muegge, as well as the contributions of Michael Olson, B.S.; George Mertz, B.S.; Katherine Marks; Kenneth Polse, O.D., M.S.; Jon Thorson, M.D.; Henry Metz, M.D.; Deborah Peltzman, B.A.; Evan Scott, B.A.; Lee Stewart, M.D.; Nancy Newman, M.D.; and Kenneth Moses, Ph.D. Finally, we thank each of our research subjects, whose anonymity must remain, for the many days of helpful service given to the study.

Through the efforts of the above-mentioned agencies, institutions, and people the results of this study were made possible. We accept responsibility for the contents of this report.

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ABSTRACT

Nine vision functions were measured by objective methods in a study sample of 19 experienced, male, marijuana users who smoked a 0.8 gram natural marijuana cigarette containing 1.5 percent (12 milligrams) of delta-9-tetrahydrocannabinol (Δ^9-THC). Placebo cigarettes were smoked as a control. The experiments were carried out double-blind with a cross-over design. Six related functions were also measured. Some of the subjects were also given 22 mg THC, alcohol, or Librium in separate experiments.

The chief results are: a) a reduction in glare recovery time with marijuana, b) a decrease in intraocular pressure with marijuana, alcohol, or Librium, c) a deterioration of tracking eye movements with alcohol, d) a rapid rise in pulse rate at the start of smoking marijuana followed by a rapid fall within minutes after smoking e) a correlation between specific subjective symptoms and objectively measured decrease in intraocular pressure, and f) a correlation between the subjects' high ratings and the intraocular pressure drop.

Some additional and incomplete results are: g) no significant change in heterophoria with marijuana, alcohol, or Librium, h) a possible reduction in amplitude, frequency, and regularity of optokinetic nystagmus with marijuana, i) no change in simple reaction time with marijuana j) a possible increase in saccadic eye movement rhythm with marijuana, k) a decrease in time production and increase in time estimation which are consistent with a "speeding up" of the internal clock after smoking marijuana, l) a suggested small decrease in pupil size after marijuana, and placebo, m) consistent conjunctival injection with marijuana, and n) suggested lid edema after smoking marijuana leading to pseudoptosis (lid droop).

I. INTRODUCTION

Despite its illegality, marijuana is used by fairly large numbers of Americans in the United States and abroad. Although the amount of the active ingredient, delta-9-tetrahydrocannibinol (Δ^9-THC), smoked by Americans in the U.S. tends to be relatively moderate (about 5 milligrams per cigarette), dosages of THC and related substances smoked by Americans abroad are much higher. The dose effects of acute and chronic THC use on most human functions are not clearly established.

Of the numerous effects reported to be associated with marijuana (THC) use, it is noteworthy than many are associated with vision. Reported vision effects can be conveniently categorized into 1) visuo-sensory effects (e.g., glare recovery time), 2) visuo-motor effects (e.g., phoria), and 3) effects on the physiology of vision (e.g., intraocular pressure). Measurements of vision effects, especially those in the first two categories, typically rely on the subject's indication of the endpoint of the test. Such subjective measurements are particularly suspect in drug studies since a drug might only affect some aspect of the subject's responsivity (such as alertness or motivation) independent of any change in the vision function. This issue of subjective responses is not trivial in the interpretation of many vision changes reported to occur with marijuana intoxication.

One approach to this problem is to devise tests that measure vision functions objectively. The use of objective tests of vision in drug studies not only has the advantage of overcoming the purely subjective effects of the drug and thereby tapping the vision function directly, but also has the advantage of leading to the possible development of a drug screening instrument if in fact the vision function exhibits unique changes following administration of specific drugs.

The long-range objective of the present study was to develop procedures for drug screening by automated vision testing. In realizing this objective it was first necessary to establish which vision functions are susceptible to objectively measured change by marijuana and other socially-used drugs, such as alcohol.

We proposed to investigate the vision functions of glare recovery time and heterophoria (phoria) for the following reasons: 1)Automatic instrumentation had already been developed in our laboratory for objective measurements of these vision functions. 2) In a widely publicized paper, Frank *et al.* (1971) reported a several second delay in subjectively measured glare recovery time following marijuana intoxication and suggested that night driving might thereby become hazardous. 3) The military implications of marijuana-induced prolongation of glare recovery are serious if personnel are hampered by an inability to recover visually from glaring light sources such as searchlights and incendiary blasts. 4) Previous preliminary work in our laboratory showed glare recovery to be unaffected by doses of alcohol large enough to produce incoherence. 5) Phoria had been frequently reported (Moses, 1970) to shift in an eso (convergent) direction under alcohol intoxication (presumably from decreased cortical inhibition of tonic midbrain activity tending to converge the eyes), and our previous preliminary studies had confirmed this result for high doses of alcohol and perhaps for marijuana. 6) Phoria shifts of only a few degrees can produce extreme discomfort and diplopia (double vision).

The instrumentation we devised for objective measurement of glare recovery employed the endpoint criterion of development of reflex optokinetic nystagmus (OKN) in response to a large field of horizontally moving vertical stripes. Previous work with this instrument suggested a possible deterioration of reflex OKN with alcohol intoxication. We, therefore, planned to investigate the possible influence of marijuana and alcohol on the quality of OKN – not only to ascertain whether the objective OKN criterion would be maintained for glare recovery measurements with these drugs but also to determine whether marijuana and/or alcohol interferes with functioning of the retino-cortical-midbrain-musculature pathways underlying OKN. For comparison of glare recovery time measured from the onset of OKN, we routinely used a subjective response of first perception of stripes as indicated by the subject depressing a button. Since such subjective measures of glare recovery time might be altered simply by changes in reaction time, we proposed a separate investigation of reaction time under marijuana and alcohol intoxication.

Thus, our originally planned research included tests of 1) glare recovery time, 2) phoria, 3) optokinetic nystagmus, and 4) reaction time. Additional functions were, for a variety of reasons, incorporated within the study once it was begun.

For example, a report (Hepler and Frank, 1971) came to our attention which indicated an average decrease of 4 mm Hg in intraocular pressure (IOP) for 11 subjects soon after they smoked a single marijuana cigarette containing 15-18 mg THC. Although the study was only preliminary, was not performed double-blind, did not include a placebo control, and did not allow for statistical significance of the results, the possible implications from the IOP decrease were nonetheless "startling." The use of marijuana (THC) for the treatment of glaucoma has already been suggested (Hepler *et al.*, 1972). Tonometric measures of intraocular pressure were therefore performed on all subjects in the study.

Objective measurement of phoria with the proposed instrumentation requires the subject to make a series of graded, horizontal, saccadic eye movements – the magnitude and reaction time of these movements being crucial to the measured phoria. It therefore seemed prudent to investigate saccadic eye movements *per se* in order to insure that the quality of these movements was sufficient after drug treatment to obtain valid phoria measurements. In addition, measurements of saccadic eye movements with the subject generating the movement rhythm from memory appeared to be a possible way of sampling the speed of his internal clock by objective means. This stimulus variation was therefore added to the measurements of saccadic eye movements. For comparison, we included subjective measures of time estimation and time production.

Within the domain of eye movement tracking are abrupt (saccadic) and smooth (pursuit) movements – two fundamentally different types of eye movement. In addition to studying saccadic eye movements (for the reasons mentioned), we decided to investigate some aspect of pursuit movements because the deterioration of OKN with alcohol in our preliminary experiments of glare recovery suggested specific involvement of pursuit movements, and because follow-up experiments in our laboratory showed that alcohol reduced the frequency of pursuit movements of a sinusoidally moving spot. The aspect of pursuit movements studied in the investigation was the frequency response of the eyes to a sinusoidally moving spot.

Three physiological indices – pupil diameter, conjunctival injection, and lid edema – were added during the study in order to confirm previous reports on these functions and to aid in the possible interpretation of other results. For example, to what extent might pupil changes account for a marijuana-induced change in glare recovery time?

Finally, we included tests which are indicants of the amount of drug absorbed into the system: the pulse rate during an experiment, the subject's evaluation of his "high" during an experiment, and a symptom check list given to each subject at the end of a day's experiment. A Breatholizer was used in the alcohol experiments to estimate blood alcohol levels.

In all, the following tests and measures were included in the investigation:

A. Glare recovery time
B. Phoria
C. Optokinetic nystagmus
D. Reaction time
E. Intraocular pressure
F. Saccadic eye movements
G. Time estimation and time production
H. Sinusoidal pursuit eye movements
I. Pupil diameter, conjunctival injection, and lid edema
J. Pulse rate
K. Subjective evaluation of "high"
L. Subjective Drug Effects Questionnaire (S.D.E.Q.)

II. GENERAL EXPERIMENTAL METHODS

The majority of the experiments were conducted in the Smith-Kettlewell Institute of Visual Sciences (SKIVS) at the Pacific Medical Center in San Francisco, California. Some of the intraocular pressure experiments were performed at the Langley Porter Neuropsychiatric Institute (LPNI) and the University of California Medical Center in San Francisco. Associated with each laboratory at SKIVS and LPNI was a special adjoining room with livingroom type furnishings (e.g., soft chairs, end tables, radio, and pictures). On an experimental day the subjects spent all of their time in this room except when they were actually being tested in the adjoining laboratory. Administration of the drug (usually marijuana, but occasionally alcohol or Librium) took place in this room.

Twenty-six subjects participated in the study. Four university students (2 male, 2 female) served as non-smoke subjects at the start of the study to develop the testing protocol. Drug experiments were performed on twenty-one males and one female (alcohol only) whose ages ranged from 18 to 37 years (average age of 24.4 years). Two subjects failed to return for their second visit, and one subject barely tolerated the intraocular pressure measurements giving erratic results which were excluded from the study. Our study sample thus consisted of 19 subjects.

The subjects had been screened by a psychiatrist to establish acceptability to the study (an experienced user having smoked marijuana at least five times, no "bad trips" on marijuana, not currently using any other drug, and not obviously emotionally unstable). They were told the general nature of the study and were given a brief description of each test to be performed. Each subject was asked to eat a light (low fat) breakfast on the day of an experiment and to arrange transportation so he would not have to drive home afterwards. The subjects generally stayed in the laboratory after the experiment until they were "down." Those who were still "high" or uncomfortable at the end of the day were sent home in a taxi. Payment for serving as a subject was $2.00 per hour plus a $10.00 bonus for a return visit.

The experiments were carried out double-blind with a cross-over design. That is, neither the subject nor the experimenter on any day knew whether the drug or placebo had been given; if marijuana (randomly chosen) was given on the first day, then placebo was given on the second day, and vice versa. One of us (R.J.) was responsible for obtaining, maintaining, preparing, assaying, and dispensing the marijuana which was grown at the U.S. Government research center in Mississippi. The placebo was prepared locally by a method described by Jones and Stone (1970).

The subjects reported to the laboratory in the morning, had electro-oculogram (EOG) skin electrodes affixed to their outer canthi and forehead (and additionally in some cases to the nape of the neck and over the radial arteries for continuous heart monitoring), and were given one or more trials on the tests to establish a pre-drug base-line. Glasses were worn if they were necessary for good distance vision; contact lenses were not worn. During an experimental day, an attending physician was either in the laboratory or was immediately available. After taking the drug, measurements were performed immediately and were repeated at regular intervals throughout the day until recovery from the drug or return to measurement base-line occurred. A light lunch was provided for the subjects at mid-day at a convenient and appropriate time between experimental trials.

The standard marijuana treatment was a 0.8 gram cigarette containing 1.5 percent (or 12 milligrams) of THC which was smoked for "maximum intake" in about ten minutes. A higher dose (22 mg THC) was used for only two subjects. The alcohol treatment was typically 0.023 ounces of 100-proof vodka per pound of weight (equivalent to 0.012 oz. of pure alcohol per lb. body weight or 0.76 ml. of pure alcohol per kilogram body weight). For a subject weighing 150 pounds, the typical dose was 3.45 ounces of 100-proof vodka. The alcohol was drunk (in about 30 minutes) with a straw in a lidded paper cup containing the alcohol, 6 ounces of water, two ice cubes, two packets of freeze-dried daquiri mix, and two drops of liquid peppermint extract. Two drops of the extract were also placed on the lid of the cup so that the alcohol and alcohol-placebo treatments looked, smelled, and tasted the same. This alcohol treatment produced blood alcohol levels of approximately 0.07 percent (as measured with a Breatholizer) 30 minutes after finishing the drink. (Blood alcohol of 0.1 percent is considered an indicant of legal intoxication in most states.) For two subjects (L.T. and C.F.), the alcohol dose was 4 ounces of 80-proof vodka (mixed with equal parts of water and two ice cubes) drunk in about 20 minutes, and followed by an additional 2 ounces of 80-proof vodka 35 minutes later. Doses of Librium were either 25 or 50 mg.

All measurements were made by or under the direct supervision of a co-investigator of the study. Tonometric measurements were performed either by an optometrist (Mackay-Marg and Goldmann tonometry) or by an ophthalmologist (Goldmann tonometry). A single examiner performed all tonometric measurements for a given subject on one instrument at a day's trial.

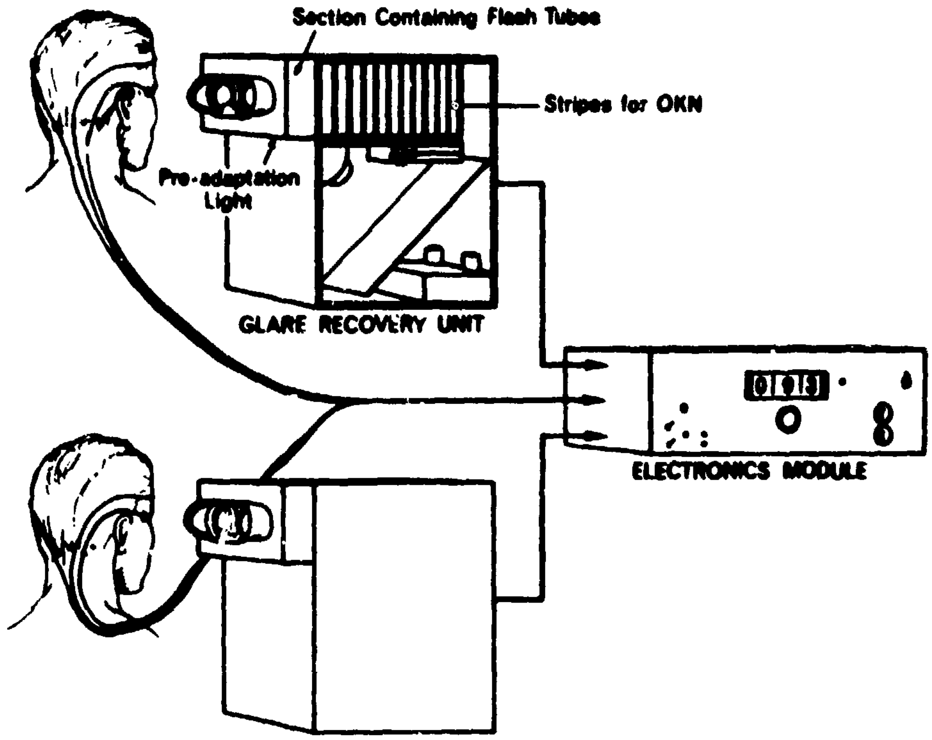

Fig. 1: Schematic representation of glare recovery and phoria test units and their interfacing to a single electronics module which also receives electro-oculographic signals from subject's eyes.

III. SPECIFIC EXPERIMENTS
A. Glare Recovery

1. *Definition and Procedure*

Glare recovery time is the period the eye takes to recover to a predetermined performance level (e.g., seeing moving stripes) after exposure to a bright gl· ·ing light.

The subject looks into a head piece and is binocularly preadapted to a uniform 100-degree by 50-degree white-light field having a luminance of approximately 1 foot lambert. Following pre-adaptation to this field, an intense uniform white light, approximately 16 joules, is briefly exposed for approximately one three-thousandth of a second. Vertical black stripes against a white background are presented in the field immediately following the glare, and optokinetic nystagmus (OKN) is generated the moment that the subject recovers from the glare and sees the stripes. The OKN is detected by Beckman surface pressure EOG electrodes and recorded in real time digital form. The onset of OKN (objective glare recovery), the subject's button press indication of when he sees the stripes (subjective glare recovery), and the automatic read out from the electronic instrumentation are all displayed on a Beckman polygraph for retrospective analysis. The apparatus is shown schematically in Fig. 1.

2. *Results and Comments*

a. Marijuana

Fourteen subjects were included in the study of glare recovery and were given both placebo and marijuana (12 mg THC) treatments on alternate days. For each test four trials of glare recovery were made and the average was taken as the measurement. All subjects were tested once or twice prior to smoking. The recovery to glare was tested 20 to 40 minutes after smoking was completed and again 1 to 3 hours post smoking. These periods are referred to as "Post 1/2" and "Post 1-3" respectively. Both objective (eye movement traces) and subjective (subject's button press) measures were recorded.

The objective glare recovery times were usually slightly longer than the subjective glare recovery times both before and after smoking marijuana or placebo. Fig. 2 depicts the pre-smoking glare recovery times of each subject

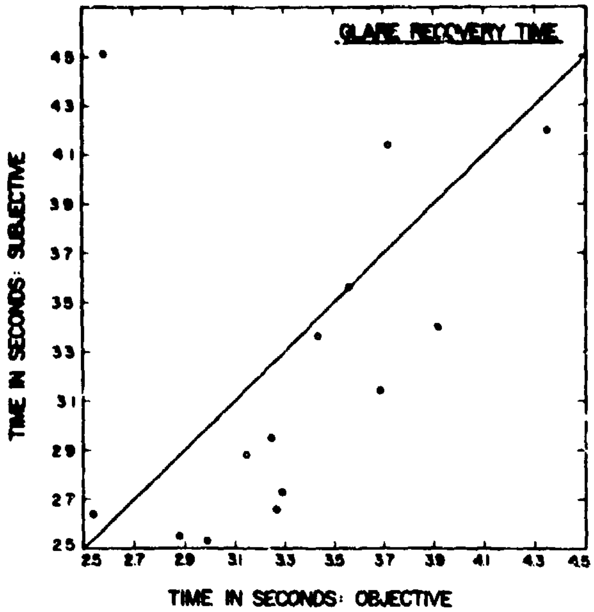

Fig. 2: Comparison of objective (OKN) and subjective (button press) recovery to glare for 14 subjects prior to smoking marijuana (6 S's) or placebo (8 S's). Identical objective and subjective glare recovery times represented by diagonal line; points below this line indicate subject perceived moving stripes before OKN was objectively evident. Data from Table I, pre-smoke condition.

on his first day of experiments (see legend to Fig. 2 for details). It will be noted that the majority of points lie below the diagonal line, signifying shorter subjective than objective recovery to glare. These results are interpreted as indicating that some vision is restored (i.e., the subject can dimly see) prior to activation of the reflex cycle of optokinetic nystagmus.

The results for each individual following marijuana and placebo are seen in Table 1 along with the group means and standard deviations. One-half hour after smoking marijuana, subjective responses of 12 of the 14 subjects indicate shorter recovery to glare, and objective recovery times were shorter in 13 subjects. In contrast, following placebo smoking, 7 subjective recovery times were shorter and 8 objective recovery times were shorter than the pre-smoke controls. The group means reflect a drop in glare recovery time both by subjective and objective measures after smoking marijuana. For the placebo condition the group means suggest no change in subjective measures and a slight increase in glare recovery time by objective measures after smoking. Fig. 3 depicts the change in objectively determined glare recovery time for each subject following placebo and marijuana smoking. All of the points above the horizontal line represent 13 of 14 subjects whose glare recovery times shortened after smoking marijuana. On the other hand, the data points to the right of the vertical line represent all of the subjects whose glare recovery time shortened after smoking the placebo. Here, only 8 of the 14 subjects are represented. Hence, if only the direction of glare recovery time changes is considered, there is a clear suggestion that marijuana smoking decreased glare recovery times. However, of more significance is the relative shift for each subject. A subject whose glare recovery time decreased both after smoking the placebo and the marijuana could have a greater decrease under marijuana conditions. This would be interpreted as a decrease in glare recovery time for the marijuana condition. Ten of the fourteen subjects had such a decrease. It should be noted that the four subjects who had a relative increase in glare recovery time after marijuana (points below the diagonal line) had extremely small relative shifts. This fact is seen by the points lying close to the diagonal line. Similar observations were made when subjective determinations of glare recovery time were used for analysis.

In determining the relative glare recovery time shift for each subject, the change which occurred under the placebo condition was used as the standard to which changes under marijuana were compared. The Walsh test of two related samples uses the relative differences in each subject in order to test the hypothesis that the mean change in objectively determined glare recovery time after smoking marijuana is significantly different from the change

Table I: Glare Recovery Time (Seconds) Measured Both Subjectively and Objectively after Smoking Marijuana (12 mg THC) or Placebo.

	MARIJUANA						PLACEBO					
	Pre-Smoke		Post Sm 1/2 hr		Post Sm 1-3 hrs		Pre-Smoke		Post Sm 1/2 hr		Post Sm 1-3 hrs	
Subject	Sub	Obj	Sub	Obj	Sub	Obj	Sub	Obj	Sub	Obj	Sub	Obj
001	3.36	3.44	3.15	3.39	3.19	3.09	2.80	2.31	3.28	2.55	2.98	3.13
002	3.56	3.56	3.45	3.68	3.32	3.45	3.70	3.43	3.70	3.56	4.05	4.41
003	4.20	4.35	3.41	3.05	3.48	3.75	3.48	3.70	3.13	2.73	3.23	3.60
004	3.10	3.40	2.85	3.08	3.40	3.50	3.14	3.69	2.96	3.43	2.88	3.25
007	2.98	3.70	3.03	3.68	3.15	3.73	4.51	2.59	3.30	4.37	3.12	2.94
010	2.88	3.42	2.18	3.22	2.88	4.10	2.73	3.29	2.66	3.06	2.47	3.0
014	3.03	3.02	3.02	2.83	2.58	2.60	2.95	3.25	2.90	3.05	2.80	2.78
015	1.97	2.49	1.76	2.19	2.53	2.61	2.53	2.99	2.44	2.92	2.33	2.85
021	4.14	3.72	3.86	3.66	3.03	2.66	2.58	2.93	3.03	2.83	3.30	3.13
022	2.66	3.59	1.95	2.80	2.34	3.03	2.88	3.15	3.26	3.93	2.93	3.97
023	2.09	2.36	1.85	2.11	1.90	2.15	2.64	2.54	2.28	2.49	2.54	3.11
024	2.66	3.27	2.43	3.20	3.09	3.35	2.59	2.83	2.93	3.27	2.99	3.26
025	2.55	2.88	2.13	2.84	2.37	2.45	2.89	2.79	2.65	2.93	3.25	3.30
026	3.12	3.80	3.58	3.78	3.21	3.17	3.40	3.92	3.82	3.80	3.25	3.53
Mean	3.02	3.36	2.76	3.11	2.89	3.12	3.06	3.10	3.02	3.21	3.01	3.30
St. Dev.	0.65	0.53	0.70	0.53	0.47	0.57	0.55	0.48	0.44	0.55	0.43	0.45

following placebo smoking. On the average, glare recovery time was longer 1/2 hour after smoking the placebo than before (3.21 and 3.10 sec., respectively) and recovery time was shorter 1/2 hour after smoking marijuana than before (3.11 and 3.35 sec., respectively). Thus, on the average, smoking the placebo resulted in 0.11 sec. *increase* in glare recovery time, and smoking marijuana resulted in a 0.25 sec. *decrease* in glare recovery time. These mean differences are significantly different at the 0.05 level (Walsh test).

In Table II the group means and medians of these *relative* glare recovery time shifts are compared to the absolute shifts represented by the means of the group data presented in Table 1. The decrease in glare recovery time is about 0.2 seconds with a range of 0.14 to 0.36 seconds, representing approximately a 7% reduction following marijuana smoking. This result holds whether objective or subjective measurements are taken, absolute or relative decreases are considered, or means or medians are used for the analysis.

This finding is important. The ability of the eye to recover from high intensity flashes or glaring light sources is extremely relevant in both military and civilian life. The earlier report that marijuana smoking increased glare recovery time (Frank *et al.*, 1971) is not supported by our study. On the contrary, there seems to be slight reduction in the time required for the eye to recover from the effects of a high intensity glare source independent of any changes in the subject's ability or desire to signal the point at which he has recovered to a standard level of vision performance. In our test the base line vision performance to which the eyes must return is relatively undemanding. It is quite possible that the change in glare recovery time following marijuana smoking may be more significantly manifested when the baseline vision performance is more demanding. In future studies we propose to explore this

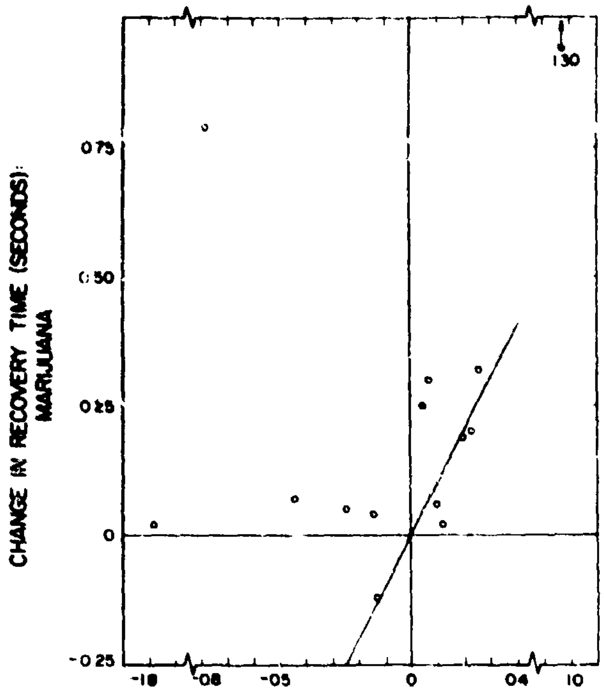

Fig. 3: Change in objective glare recovery time following marijuana compared with change following placebo. Each point represents change in one subject's recovery times pre- and 1/2 hour post-marijuana (ordinate) and pre- and 1/2 hour post-placebo (abscissa). Horizontal line represents no change in recovery time after marijuana; points above (13 of 14) indicate shorter glare recovery after marijuana than before. Vertical line represents no change between pre- and post-placebo; points to right (8 of 14) indicate shorter glare recovery after placebo than before. Diagonal line indicates same change following both marijuana and placebo; points above diagonal indicate "relative decrease" in glare recovery time after marijuana (10 subjects).

hypothesis. Meanwhile, our results suggest that marijuana smoking is unlikely to effect detrimentally the eyes' ability to recover from blinding light flashes.

It is not clear why glare recovery time should be reduced following marijuana smoking. However, it does not appear to be related to the slight constriction of the pupil noted after smoking marijuana. This constriction amounts to a reduction of pupil diameter of approximately 0.2 mm. Assuming a 4 mm pupil, this corresponds to a reduction of pupil area by about 10%. Consequently, a corresponding reduction in retinal illumination is anticipated (ignoring the Stiles-Crawford effect). The 10% reduction occurs for the pre-adapting light, the glare flash, and the average luminance of the stripe test grating. The contrast and luminance of the test grating are sufficiently high that a 10% reduction in effective retinal illuminance is insignificant. A 10% reduction in the pre-adapting luminance used in this study is not capable of producing significant changes in the glare recovery times, as was determined on this instrumentation prior to this contract. Any effective reduction in pre-adapting luminance would be expected to produce *longer* glare recovery times. The most obvious way to test this idea is to produce the same reduction in control subjects by application of 10% reducing neutral density filters in the eyepieces of the instrument. We do not expect this reduction to produce a decrease in glare recovery times comparable to that seen following marijuana smoking. Other possible explanations can be presented for the decreased recovery time, including an increased retinal blood flow to the retina (similar to the increased flow to the conjunctiva, cf. Section Ib). At this point we have no quantitative evidence to support this latter speculation.

Table II: Average Decrease in Subjective and Objective Measures of Glare Recovery Time (Seconds) for Fourteen Subjects 1/2 Hour after Smoking Marijuana (12 mg THC); Absolute Times (Above) and Times Relative to Placebo Change (Below).

		Objective	Subjective
Absolute	Mean	0.25 sec.	0.26 sec.
	Median	0.14 sec.	0.24 sec.
Relative	Mean	0.36 sec.	0.23 sec.
	Median	0.19 sec.	0.15 sec.

b. Alcohol

Three subjects were tested after drinking alcohol (0.012 oz./lb. body wt.) in one dose over a 30 minute period. One of the subjects was given a placebo drink on a second day amd was told that it was "a different dose level." Again, each subject's glare recovery time was measured objectively and subjectively prior to and following the drink. As seen in Table III, all three subjects showed an increase in their objectively determined glare recovery measures 1/2 hour post ingestion. Two of the three subjects showed a similar increase in their subjectively determined glare recovery measures. The one subject who was given the placebo showed a very slight decrease in both subjectively and objectively determined glare recovery in contrast to his *increased* times after drinking alcohol. The means and standard deviations for the group are seen in Table III together with the individual results. With so few subjects it is difficult to draw conclusions. Certainly statistical significance cannot be attained on such a small group. It would be worthwhile to pursue this experiment on a larger group of subjects at more than one vision performance level, particularly since a reduction in glare recovery time has considerable practical relevance in both military and civilian life.

c. Librium

Three subjects were each given 50 mg of Librium; their glare recovery times were measured prior to and following the Librium treatment. One of the subjects was given 25 mg of Librium on a second day. For all subjects glare recovery time increased slightly (about 0.2 seconds) especially 1 hour following the ingestion of Librium. This increase was apparent for both objective and subjective measurements. Because of the small group it is not possible to attach statistical significance to the change, but the trend of the result is of considerable interest and should be explored in a larger group. Table III presents the group means and standard deviations together with the individual results.

B. Heterophoria

1. *Definition and Procedure*

Heterophoria is a latent deviation of the eyes which becomes manifest when binocular fused vision is disrupted. For example, when a heterophoric subject is binocularly fixating a point in space and a card is placed before one eye, that eye will then rotate to its phoria position (nasalward = esophoria; temporalward = exophoria). Movement of the card to the other eye will result in a conjugate movement of the eyes. The direction of this conjugate movement is that of the deviating eye from its phoria position to the fixation point. The heterophoria (phoria) reflects the oculomotor imbalance, which is the result of the tonic inputs that contribute to extraocular muscle

Table III: Glare Recovery Time (Seconds) Measured Both Subjectively and Objectively after Ingestion of Alcohol (0.012 oz/lb) or Librium (25 or 50 mg).

ALCOHOL

Subject	Pre-Drink Sub	Pre-Drink Obj	Post Dr 1/2 hr Sub	Post Dr 1/2 hr Obj	Post Dr 1-3 hrs Sub	Post Dr 1-3 hrs Obj
004	2.85	3.25	3.20	3.40	3.23	3.83
014	2.48	2.52	2.97	3.47	2.55	3.15
023	2.15	2.37	1.77	2.48	2.05	2.25
Mean	2.49	2.71	2.65	3.12	2.61	3.08
St. Dev.	0.35	0.47	0.77	0.55	0.59	0.79

ALCOHOL PLACEBO

Subject	Pre-Drink Sub	Pre-Drink Obj	Post Dr 1/2 hr Sub	Post Dr 1/2 hr Obj	Post Dr 1-3 hrs Sub	Post Dr 1-3 hrs Obj
014	2.77	3.08	2.60	3.02	2.67	3.20

LIBRIUM 50 mg.

Subject	Pre-Ingest. Sub	Pre-Ingest. Obj	Post 1 hour Sub	Post 1 hour Obj	Post 3 hours Sub	Post 3 hours Obj
004	3.04	3.23	3.20	3.45	3.30	3.80
014	2.63	3.00	2.75	3.25	2.75	2.95
023	1.50	1.35	1.78	2.42	1.52	1.80
Mean	2.39	2.53	2.58	3.04	2.52	2.85
St. Dev.	0.80	1.03	0.73	0.55	0.91	1.00

LIBRIUM 25 mg.

Subject	Pre-Ingest. Sub	Pre-Ingest. Obj	Post 1 hour Sub	Post 1 hour Obj	Post 3 hours Sub	Post 3 hours Obj
014	2.70	3.15	2.90	3.40	2.53	2.97

tonus. Phorias can be changed by certain drugs, peripherally by homatropine and systemically by barbiturates, alcohol, and anoxia (Ogle *et al.*, 1967). The general principle employed in measuring phorias is to move the target (as seen by each eye) either physically or optically until alternate exposure of the target results in no eye movement. This null principle, used in virtually all phoria measurements, is also used in the present instrument to measure horizontal phorias and to detect possible phoria changes.

The stimulus array and presentation method in our instrument are unique. The left eye fixates a small (about 10 min. arc) pinlight at optical infinity in the left half-field of a 10-diopter stereoscope (cf. Fig. 1). This target is extinguished and a similar pinlight target is immediately exposed to the right eye at some lateral eccentricity from the optical axis of the stereoscope lens. The movement of the right eye required to move from its phoria position to fixate the pinlight is measured objectively by electro-oculography (EOG). The process is repeated (left eye's light, right eye's light) with the right eye's light being randomly positioned over the range of 15 esophoria to 15 exophoria in 2 prism diopter steps. The phoria is "measured" (and displayed) when the EOG signal indicates no movement required of the right eye to fixate a certain light (or lights).

The total time required to complete this test is about one minute. Only during the time defined by the extinction of the left light and the extinction of the right light are null movements sought. Any eye movements which take place during the time required for sustained fixation of a light are ignored.

2. *Results and Comments*

a. Marijuana

Fourteen subjects, studied in a "double-blind" experiment, were given both placebo and marijuana treatments. At each test four measures of phoria were made, and the average was taken as the phoria. Subjects were

Table IV: Phoria (Prism Diopters) Measured Objectively for Optical Infinity after Smoking Marijuana (12 mg THC) or Placebo; Esophoria "+," Exophoria "-."

	MARIJUANA			PLACEBO		
Subject	Pre-Smoke	Post Sm 1/2 hr	Post Sm 1-3 hrs	Pre-Smoke	Post Sm 1/2 hr	Post Sm 1-3 hrs
001	+1.7	+1.8	+1.2	-1.4	+2.0	0
002	+3.8	+2.3	+2.8	+3.0	+2.8	+2.25
003	+8.5	+8.7	+5.5	+9.7	+10.0	+9.5
004	+9.0	+9.3	+7.6	+7.3	+6.6	+6.6
007	+1.5	-0.3	0	+1.5	+2.0	+1.67
010	+8.8	+8.5	+8.8	+11.4	+9.6	+9.7
014	+1.6	+5.0	+3.9	+2.3	+2.0	+3.3
015	+0.5	-1.9	-0.4	+1.0	-0.8	-0.3
021	+6.6	+4.5	+2.5	+2.8	+3.9	+4.5
022	+9.0	+6.8	+6.7	+8.9	+8.4	+7.1
023	+8.0	+8.0	+8.6	+8.4	+8.1	+5.4
024	+5.1	+4.3	+5.0	+6.6	+6.5	+6.1
025	+6.4	+7.8	+6.4	+7.2	+6.5	+5.8
026	+3.3	+4.3	+5.2	+3.5	+2.50	+4.0
Mean	5.27	4.94	4.56	5.16	5.01	4.69
St. Dev.	3.17	3.50	3.01	3.82	3.37	3.11

tested once or twice prior to smoking. The phoria was tested 20 to 40 minutes following completion of the smoking and again between 1 to 3 hours following smoking. These periods have been referred to as "Post 1/2" and "Post 1-3," respectively, in Table IV where the results for each subject are presented.

Because of the large individual differences in baseline phoria between subjects, the standard deviations for the group are large and consequently no statistical significance (at 0.05 level) can be attached to the differences between pre and post conditions for either the marijuana or placebo smoking. Further, the mean *change* in phoria after smoking marijuana is not significantly different (at the 0.05 level) from the mean *change* in phoria after smoking placebo (Walsh related sample test).

It will be noted that the mean pre-smoke phorias are of the order of +5 prism diopters. This value reflects a baseline bias of our instrumentation, as will be discussed below relative to proximal convergence. However, since the effects of smoking are expressed in terms of each subject's relative shift with respect to his own baseline, the absolute levels need not be considered.

One-half hour after smoking marijuana, seven of the subjects showed a shift toward exophoria (mean = 1.8 prism diopters) while six of the subjects showed a shift toward esophoria (mean = 1.1 prism diopters) (Fig. 4). After smoking the placebo, ten of the subjects had an exophoria shift (mean = 0.7 prism diopters) while four of the subjects had an esophoric shift (mean = 1.3 prism diopters).

Of interest is the phoria shift each individual makes with respect to his own change under the placebo condition. If a subject showed a greater esophoric shift under marijuana than under the placebo condition, then the shift could be referred to as a "relative esophoric shift" under marijuana. Fig. 4 illustrates the phoria shifts in each of the

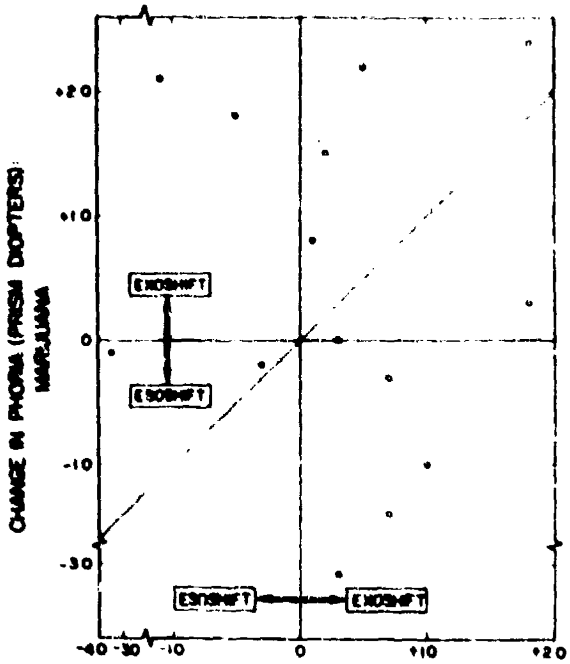

Fig. 4: Change in objectively measured distance phoria for 14 subjects 1/2 hour after smoking marijuana compared to change after smoking placebo. The 8 points above diagonal line represent relative exoshift after marijuana compared to placebo.

subjects 1/2 hour after the marijuana and placebo treatments. It can be seen that 8 of the 14 subjects showed a relative exophoric shift, as reflected by the data points which fall above the diagonal line, indicating relatively more exophoric shift under marijuana than in the placebo condition.

Thus, in our experiment there appears to be no clear trend in phoria shift following marijuana smoking. Of course, this result may not be true for a larger group or for higher doses of Δ^9-THC.

Moskowitz *et al.* (1972) using 12 subjects, have suggested that there is a slight esophoric shift in subjects after smoking approximately the same THC dosage of marijuana as was used in our study. The distance phoria was measured in both studies. They used a target 20 feet from the eyes and a subjective clinical technique. In our study, the stimuli were optically at infinity but were physically at 10 centimeters from the subject's eyes, and the phoria was determined objectively.

When a subject is aware that the targets are physically close, he tends to converge his eyes even though the targets are optically at infinity. This phenomenon is often referred to as proximal convergence which is generally considered to be relatively stable in a given instrument and subject. Our previous nondrug studies on this instrument suggested that proximal convergence was not only stable but relatively constant between subjects (approximately 4 prism diopters of convergence). However, it is possible that drugs like marijuana may alter the proximal convergence by increasing or decreasing it. In our experiments a decrease in proximal convergence after smoking marijuana may mask a distance esophoric shift. While we have no indication that this happened in our experiments, it is a possible explanation of the discrepancy between our results and those of Moskowitz *et al.* (1972). Since presmoke levels covered such a wide phoria range, the possibility also exists that a group of 12 to 14 subjects may not be sufficient to show a general trend.

b. Alcohol

Phoria measurements were made on five subjects before and after they received alcohol. Three of the subjects were given a single dose of 0.012 oz. alcohol/lb. body weight which they drank over a period of about 30 minutes. Blood alcohol measurements were made 30 minutes and one hour after ingestion was completed. For these

Table V: Phoria (Prism Diopters) Measured Objectively for Optical Infinity after Drinking Alcohol (0.012 oz/lb) or Placebo; Esophoria "+," Exophoria "-."

	ALCOHOL			PLACEBO		
Subject	Pre-Alcohol	Post 1 Hr.	Post 2 1/2 Hr.	Pre-Alcohol	Post 1 Hr.	Post 2 1/2 Hr.
004	+6.8	+7.9	+9.8	--	--	--
012	+6.0	+4.8	+5.0	--	--	--
013	+4.5	+6.0	+4.5	--	--	--
014	+4.0	+5.0	+5.0	+2.6	+3.8	+1.73
023	+8.2	+6.7	+9.8	--	--	--
Mean	+5.89	+6.07	+6.81			
St. Dev.	1.70	1.26	2.71			

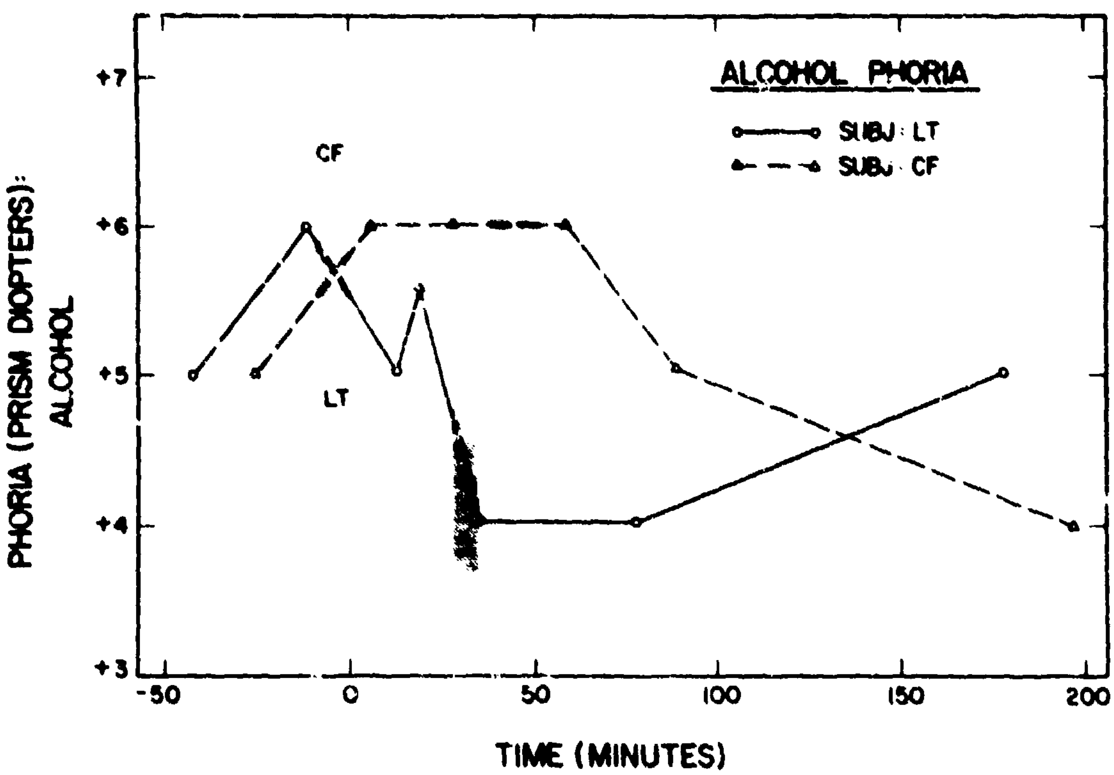

Fig. 5: Time course of objectively measured distance phoria with alcohol. First drink was 4 oz.; second, 2 oz. of 80 proof alcohol; shaded areas represent ingestion periods.

Table VI: Phoria (Prism Diopters) Measured Objectively for Optical Infinity after Librium Ingestion (25 or 50 mg); Esophoria "+," Exophoria "-."

	LIBRIUM 50 mg.			LIBRIUM 25 mg.		
Subject	Pre Librium	Post 1 Hr.	Post 2 1/2 Hr.	Pre Librium	Post 1 Hr.	Post 2 1/2 Hr.
004	+8.1	+6.6	+8.0	--	--	--
014	+4.3	+3.5	+3.8	+1.6	+2.7	+2.2
023	+10.4	+9.4	+10.5	--	--	--
Mean	+7.60	+6.50	+7.45			
St. Dev.	3.08	2.95	3.40			

three subjects the blood alcohol levels were close to 0.07% after 30 minutes. The other two subjects were given two doses of alcohol: 4 oz. of 80-proof alcohol initially (taken over a period of fifteen minutes) and a subsequent dose of 2 oz. of 80-proof alcohol approximately 35 minutes after finishing the first drink. Blood alcohol levels were not recorded for these two subjects.

Table V shows the results for the five subjects. Within one hour after drinking alcohol, three of the subjects showed an esophoric shift (mean = 1.2 prism diopters) and two showed an exophoric shift (mean = 1.35 prism diopters). The alcohol placebo was used for one subject. Under this condition the subject showed an exophoric shift 1 hour post ingestion.

For the two subjects who were given two doses of alcohol, the phoria was measured a number of times during the experiment. Fig. 5 depicts the time course of their phoria measurements. One subject (C.F.) developed an esophoric shift, the other (L.T.) an exophoric shift.

The variable directions of shift in our five subjects are not consistent with the results generally reported. In the literature, the consensus is that the distance phoria almost always shifts toward esophoria (Moses, 1970).

c. Librium

Three subjects were given 50 mg of Librium and their phoria was tested pre and post ingestion. For one subject, the phoria measurements were repeated on a second day before and after administration of 25 mg of Librium. Within one hour after ingestion of 50 mg Librium, all three subjects showed an exophoric shift (mean = 1.1 prism diopters); two of the subjects showed a return to their pre-Librium phoria levels within 3 hours of ingestion. Table VI lists the results for each subject.

C. Optokinetic Nystagmus

1. *Procedure and Comment*

The onset of optokinetic nystagmus (OKN) was used as a measure of the objective glare recovery time. The details of this test and the role of OKN are discussed above in Specific Experiments, Section A. Our preliminary experiments in a previous study (Jampolsky *et al.*, 1970) suggest that the quality of OKN deteriorated markedly after a high dose of alcohol. The OKN became very irregular. Using a relatively high dose of marijuana (22 mg THC), we noticed similar but less marked changes in one subject. The problem of quantifying OKN performance is nontrivial, since amplitude, frequency, and consistency could be used alone or in various combinations as the performance criterion.

2. *Results*

Our preliminary qualitative analysis suggests that after smoking marijuana some subjects exhibit noticeably reduced amplitude, velocity, and frequency of saccadic eye movements in their OKN. Many subjects had less regular OKN.

Table VII: Mean Reaction Time (Milliseconds) to Signal Lamp for Randomized Delays for 2, 3, 4, and 5 Seconds Combined; Marijuana (12 mg THC) and Placebo Treatments.

	MARIJUANA			PLACEBO		
SUBJECT	Pre Smoke	Post 1/2 hr	Post 1-3 hr	Pre Smoke	Post 1/2 hr	Post 1-3 hr
001	222.3	264.1	274.9	237.8	244.3	194.1
002	254.0	248.4	249.1	236.3	247.5	256.3
003	231.1	262.7	261.0	234.0	245.0	221.0
004	221.8	234.4	227.5	194.4	221.1	190.6
007	275.1	260.9	254.0	248.5	271.9	282.4
010	236.0	202.5	210.1	224.1	213.0	197.9
014	330.5	305.6	308.0	318.4	304.3	316.9
015	274.9	275.1	269.4	262.0	323.0	308.3
021	258.8	292.9	296.9	280.8	256.6	264.8
022	291.4	291.3	276.8	265.8	252.6	295.9
023	250.9	252.3	225.5	248.1	268.0	260.8
024	233.9	282.9	256.6	248.5	240.5	253.5
025	277.9	258.4	284.4	267.4	259.9	277.6
026	298.5	301.9	330.8	283.6	382.4	317.5
Mean	261.22	266.67	266.07	253.55	266.58	259.83
St. Dev.	31.96	28.02	33.11	29.92	44.12	44.37

D. Reaction Time

1. *Procedure*

Objective recording of a subject's simple reaction time in releasing his index finger from a button following the onset of a light bulb was measured for pre-determined delay times of two, three, four, and five seconds. The presentation of the delay times was randomized, thus preventing the subject from anticipating when the onset of the light would occur. A total of eight trials (each delay time presented twice) was involved at each sitting. Release of the finger from the button stopped a clock; the reaction time was recorded in milliseconds. Simple reaction time was measured before and after drug and placebo administration. Tests were made 20 to 45 and 60 to 180 minutes following the drug treatment.

Two forms of data analysis were employed. The first involves the recording of the mean reaction time for the

Table VIII: Percentage Change in Reaction Time for Randomized Delays of 2, 3, 4, or 5 Seconds in Signal Lamp; Marijuana (12 mg THC) and Placebo Treatments.

	MARIJUANA				PLACEBO			
SUBJECT	Delay 2 sec	Delay 3 sec	Delay 4 sec	Delay 5 sec	Delay 2 sec	Delay 3 sec	Delay 4 sec	Delay 5 sec
001	+0.7	-47.1	-7.9	-30.9	-17.4	+16.9	-12.1	+2.0
002	+16.0	-12.8	+0.4	+8.6	+10.9	-13.0	-22.0	-4.4
003	-25.5	-15.4	-6.9	-8.5	+7.0	-0.4	-18.6	-9.8
004	-11.3	-6.9	+11.3	-18.4	-28.2	-31.1	+1.5	+0.5
007	0	+6.7	+12.1	+1.1	-40.1	-14.2	+15.6	-2.3
010	+10.8	+20.0	+9.6	+15.8	-2.0	+29.8	-10.5	+14.9
014	+1.2	+23.7	-1.6	+3.7	-29.4	-3.0	+12.5	+5.2
015	+9.2	-3.4	-2.5	-4.0	-27.3	-38.9	-25.1	-6.6
021	+4.7	-32.2	-42.8	+1.8	+17.9	-5.7	-3.7	+18.3
022	+15.7	+19.4	-4.5	+3.4	+9.7	-31.5	+12.7	+23.5
023	-8.7	-5.6	+12.5	-2.6	-10.1	-9.2	+13.5	-28.8
024	-12.1	+5.3	-14.7	-42.4	+11.1	+0.9	-18.9	+12.2
025	-1.5	+6.7	+8.6	+13.4	-15.6	+13.0	+0.8	+11.7
026	+2.9	-8.4	-6.6	-11.2	-9.3	-16.1	-47.6	-86.0
Mean	+0.15	-6.34	-2.36	-5.01	-8.77	-7.32	-7.28	-3.54
St.Dev.	11.56	19.03	14.54	16.39	18.36	19.26	18.31	27.23

pre- and post-drug treatments. The second involves the percentage change in the reaction time when the pre- and post-drug reaction times are compared as follows: 100 (Pre-Post)/Pre. Using this form of analysis, the percentage change in reaction time can be calculated for each delay time alone or for all delay times collectively (8 trials).

2. *Results and Comments*

a. Marijuana

Reaction time experiments were performed on 14 subjects for both placebo and marijuana treatments. The mean reaction times of each subject for all delay times combined are presented in Table VII together with the group means and standard deviations. There is no significant change in reaction time for the group after smoking placebo or marijuana.

The percentage *change* in reaction time after smoking was calculated for each subject for each delay period. The results are shown in Table VIII and are illustrated graphically in Fig. 6. Again, there is no apparent change in reaction time for the group even when the results are considered as a percentage change for each of the delay times.

These results are consistent with other reports for simple reaction time experiments done in conjunction with marijuana smoking. Most of the literature suggests that little or no change in simple reaction time occurs after smoking marijuana. However, when the task is complex or unfamiliar, changes in reaction time are reported (Weil, *et al.*, 1968; Moskowitz *et al.*, 1972). We originally included the reaction time experiments as a control for our glare recovery experiments, reported in Section A above. If subjectively determined glare recovery times had been longer

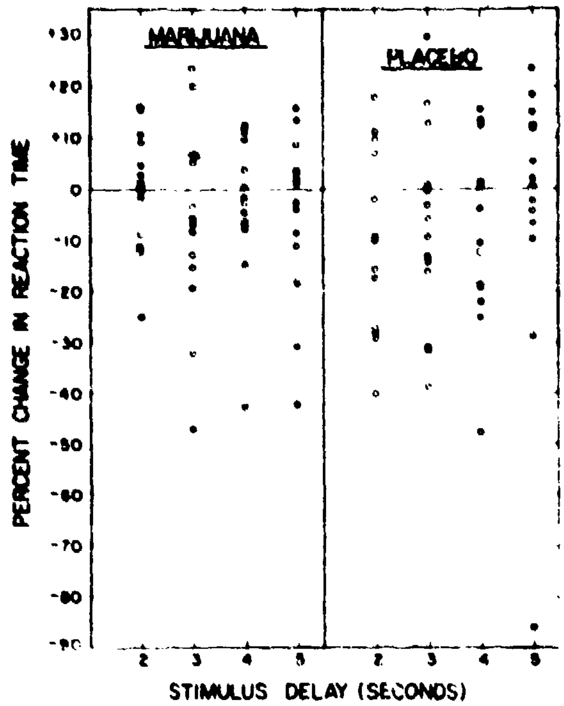

Fig. 6: Percentage change in reaction time 1/2 hour after smoking marijuana and placebo compared to pre-smoke values; each of 14 subjects was tested using 4 delays in the light stimulus.

than our objectively determined times, then we would need to know if the longer times were related to a change in button press reaction time. As has already been shown, subjective glare recovery times tended to be shorter than objective times; the results of our reaction time experiments are therefore not crucial in the analysis of glare recovery time data.

b. **Alcohol**

Reaction time experiments were performed on three subjects using the same dose used in the glare recovery task (0.012 oz./lb. body weight). The results are presented in Table IX, and suggest that simple reaction time is only slightly altered in each subject. Two of the three subjects showed an increase in reaction time following alcohol intoxication. There is no significant trend for the group although the group reaction time is slightly longer 1/2 hour after drinking alcohol.

c. **Librium**

Three subjects were given oral doses of Librium under the same conditions as outlined for the glare recovery task. As with the alcohol, there is no significant change in reaction time for the group. The results for each subject are shown in Table IX.

E. Intraocular Pressure

1. *Procedure and Comment*

The pressure within the human eye (about 15.5 mm Hg) helps the eye maintain its spherical shape and provide nutriment flow to its tissues. Elevated intraocular pressure is associated with the disease glaucoma wherein irreversible loss of vision can occur. Ocular hypotension is often associated with uveitis and retinal detachment (Moses, 1970).

Intraocular pressure (IOP) was measured on all subjects with a Mackay-Marg electronic tonometer and on some subjects with a Goldmann tonometer for comparison. One drop of 0.5 percent Ophthaine was used for topical anesthetic with both instruments; fluorescine was also used with the Goldmann tonometer. When Goldmann tonometry was used, it was performed before Mackay-Marg tonometry. The right eye was always measured first.

Table IX: Mean Reaction Time (Milliseconds) to Signal Lamp for Randomized Delays of 2, 3, 4, and 5 Seconds Combined; Alcohol (0.012 oz/lb) and Librium (25 and 50 mg) Treatments.

	ALCOHOL			PLACEBO		
SUBJECT	Pre-Ingest.	Post 1/2 hr	Post 1-3 hr	Pre-Ingest.	Post 1/2 hr	Post 1-3 hr
004	207.1	236.5	230.8			
014	300.4	289.8	276.3	274.4	272.3	279.5
023	232.0	243.0	223.9			
Mean	246.5	256.43	243.67			
St.Dev.	48.31	29.08	28.47			
	LIBRIUM - 50 mg.			LIBRIUM - 25 mg.		
004	211.8	226.3	204.8			
014	285.4	259.4	288.0	259.3	280.0	264.1
023	218.1	204.4	213.9			
Mean	238.43	230.03	235.57			
St.Dev.	40.80	27.69	45.64			

Between five and ten measurements (tonograms) were taken on each eye with the Mackay-Marg tonometer, and three measures with the Goldmann. For the group data, the IOP was taken as the mean of the three tonograms having the best waveforms and giving the lowest consistent readings. For comparison of IOP within individuals, the mean of all readings was used for Mackay-Marg and Goldmann tonometry.

On a given day, several sets of tonometry readings were taken about twenty minutes apart before the drug was administered. In the marijuana experiments, tonometer readings were routinely obtained approximately 5, 30, 80, 120, and 180 minutes after smoking.

Fifteen subjects participated (double blind) in the IOP experiments, each subject receiving the 12 mg THC and placebo treatments randomly on alternate days. Six of the subjects returned on other days for higher dose (22 mg THC) experiments, Goldmann comparison experiments, or alcohol and Librium experiments.

2. *Results and Comments*

a. Marijuana

Table X shows the Mackay-Marg tonometry measurements for the right eyes of 15 subjects given 12 mg THC and placebo. The mean pressures before smoking were slightly lower for marijuana (14.6 mm Hg) than for placebo (15.2 mm Hg). Comparison of IOP for the two treatments at the same time periods after smoking shows a greater number of lower pressures as well as greater post-smoke decreases for marijuana than placebo. Thirteen of the 15 subjects exhibited decreased IOP following marijuana, with the lowest pressures being recorded 5 min. post in 2 subjects; 30 min. post in 3; 80 min. post in 2; 120 min. post in 5; and 180 min. post in one subject. Combining

Table X: Intraocular Pressure (mm Hg) after Smoking Marijuana (12 mg THC) or Placebo.

SUBJECT	MARIJUANA Pre-5 min	Post 5 min	Post 30 min	Post 80 min	Post 120 min	Post 180 min	PLACEBO Pre-5 min	Post 5 min	Post 30 min	Post 80 min	Post 120 min	Post 180 min
003	11.8	11.0	9.8	7.2	10.2	10.5	15.5	12.5	15.2	15.3	15.8	15.7
004	14.3	12.5	12.3	10.8	13.5	11.5	11.5	12.7	13.2	12.0	9.3	11.3
005	14.8	19.0	16.2	15.3	13.7	15.7	16.3	14.3	17.2	15.3	17.6	15.7
007	20.0	14.0	18.7	19.3	16.3	17.7	18.0	17.5	15.0	18.3	16.5	19.2
008	14.3	11.5	13.8	12.5	10.5	12.7	12.3	18.5	13.0	14.2	14.3	--
010	13.3	9.3	6.9	8.4	10.4	10.5	12.0	12.0	13.5	12.5	15.2	14.0
011	17.7	15.0	15.2	16.7	18.5	21.7	15.3	18.5	18.3	16.8	20.6	18.7
014	15.2	13.2	12.7	12.0	11.7	15.5	19.7	16.3	18.7	20.3	19.3	--
015	13.5	16.3	15.5	14.8	16.0	14.0	19.2	14.3	16.0	17.8	19.3	18.3
021	17.5	11.5	13.7	13.5	13.5	12.0	14.0	11.5	12.3	9.8	12.7	13.0
022	12.7	11.3	9.8	10.0	8.7	10.0	12.0	14.8	13.8	14.5	10.3	15.3
023	12.3	11.2	10.2	10.7	11.2	13.8	15.2	12.5	12.5	10.8	8.5	10.3
024	13.2	13.0	13.3	12.7	11.7	13.2	13.3	12.0	12.0	14.0	15.6	15.8
025	14.7	10.0	10.5	10.3	13.5	9.5	16.0	15.5	13.3	13.0	10.2	10.7
026	13.3	16.3	14.2	13.8	17.3	14.3	17.0	16.0	14.2	17.2	16.5	15.3
Mean	14.6	13.0	12.9	12.5	13.1	13.5	15.2	14.6	14.5	14.8	14.8	14.9
Diff.		-1.6	-1.7	-2.1	-1.5	-1.1		-0.6	-0.7	-0.4	-0.4	-0.3
% Diff.		-10.9	-11.6	-14.3	-10.2	-7.5		-3.9	-4.6	-2.6	-2.6	-1.9
St.Dev.	2.3	2.7	3.0	3.2	2.9	3.3	2.6	2.4	2.1	2.9	3.8	2.9

data from all subjects indicates that the greatest mean drop from baseline levels is 2.1 mm Hg., representing a mean decrease of 14.3 percent. Corresponding results are noted for the placebo at 30 minutes with a decrease of 0.7 mm Hg (4.6 percent decrease). Visualization of the comparative IOP time courses for the two treatments is provided in Fig. 7 where the mean IOP values for placebo have all been reduced by 0.6 mm Hg to equate the mean pre-smoke pressure (15.2 mm Hg) with that for marijuana (14.6 mm Hg). In essence, the placebo IOP curve has been lowered on the graph (Fig. 7) so that the pre-smoke mean pressures coincide.

The distribution of the group IOP measures at any test time is indicated by the standard deviations (Table X) which range from 2.1 to 3.8 mm Hg and average between 2.8 and 2.9 mm Hg for both treatments. In the face of standard deviations of this magnitude, it seemed unlikely that a 1.7 mm Hg difference between the two curves at 80 minutes after smoking would be statistically significant. Indeed, the Walsh test (Siegel, 1956), a powerful nonparametric alternative to the t-test, indicates that the group marijuana and placebo curves (Fig. 7) are not significantly different (at the 0.05 level) at the 80-minute or at any other post-smoke test time.

What is of fundamental interest is the *pre- vs. post-smoke change in pressure resulting from marijuana compared to placebo.* Table XIa shows these changes in IOP; minus numbers indicate a larger drop in pressure after smoking marijuana than placebo. Statistical analysis by the Walsh test (Siegel, 1956) indicates that the comparative changes in IOP are not significant at the 0.05 level for any test time except at 80 minutes post-smoke where the 1.7 mm Hg greater drop in pressure with marijuana is significant at the 0.02 level. While a relative (marijuana vs. placebo) mean decrease of 1.7 mm Hg in IOP 80 minutes after smoking is statistically significant, this decrease may be practically (or clinically) insignificant. Indeed, diurnal variations in IOP are at least twice as large. A relevant question is whether the several large, individual post-smoke IOP decreases are repeatable and, if so, whether such decreases are characteristic of the subject or of some response to the marijuana. Most of the remaining aspects of this IOP study were directed at this question.

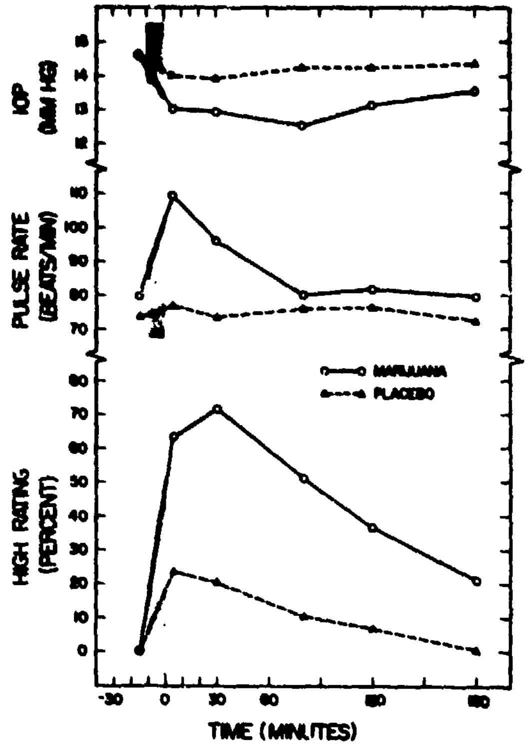

Fig. 7: Time course of mean intraocular pressure, pulse rate, and subjective high rating for 14 subjects who smoked marijuana or placebo (shaded area).

As will be documented below in Section J, pulse rates peaked on the average about 5 min. post marijuana and were essentially normal by 80 min. post. Further, as is documented in Section K, mean "high" ratings were highest 30 min. post marijuana. These results are presented in Fig. 7 for comparison with the mean IOP time course. It will be noted that within 5 minutes after smoking marijuana, the mean IOP had dropped to about 75 percent of its minimum, and the average "high" rating reached about 90 percent of its maximum. Physiological and psychological effects of the marijuana were fully or nearly fully demonstrable within 5 minutes after smoking marijuana. Parenthetically, the same observation was true for the placebo, where lesser changes followed a similar time course.

Of special interest is the finding that the mean IOP was at its minimum at a time (80 minutes post-marijuana) when the mean pulse rate had already returned to pre-smoke base-line, but the mean high rating was still at about 70 percent of its maximum (Fig. 7). In other words, IOP showed an early decrease that was sustained for two hours; the pulse rate exhibited an immediate increase but was back to normal by 80 min.; the "high" rating showed an early rapid rise and a slow decline during the second and third hours after marijuana. These results suggest that the marijuana-induced IOP decrease may be associated more with the "high" than with blood THC as indicated by pulse rate (Galanter *et al.*, 1972). Additional support for this notion is the return to base-line value of both IOP and high rating at about four to five hours after marijuana.

Other investigators (Moses *et al.*, 1962) have established a high correlation (+0.93) between IOP measurements made on different subjects with the Goldmann and Mackay-Marg tonometers. Nonetheless, for several subjects in the present experiments, both tonometers were used in order to rule out possible systematic measurement error with the Mackay-Marg tonometer. Both tonometers indicated similar IOP measures for each subject tested. An example is shown in Fig. 8 where the readings from the two tonometers are significantly correlated for both marijuana and placebo (r_s = +0.86 and +0.81, respectively; N = 7 and N = 8; $p < 0.05$).

Because Subject R.S. (003) showed such a clear-cut decrease in IOP with marijuana and relative stability of IOP with placebo, it was decided to have him return in order to ascertain the repeatability of the marijuana-IOP effect. Fig. 9 shows the results for three pairs of trials, the control (placebo or no-smoke) curve in each case being

Table XIa: Change in Intraocular Pressure (mm Hg) after Smoking Marijuana (12 mg THC) Relative to Change in Pressure after Smoking Placebo; Negative Numbers Indicate Larger Pressure Drop after Smoking Marijuana than Placebo.

(Post Marijuana-Pre Marijuana) - (Post Placebo-Pre Placebo)

SUBJECT	Post 5 min	Post 30 min	Post 80 min	Post 120 min	Post 180 min
003	+2.2	-1.7	-4.4	-1.9	-1.5
004	-3.0	-3.7	-4.0	+1.4	-2.6
005	+6.2	+0.5	+1.5	-2.4	+1.5
007	-5.5	+1.7	-1.0	-2.2	-3.5
008	-9.0	-1.2	-3.7	-5.8	--
010	-4.0	-7.9	-5.4	-6.1	-4.8
011	-5.9	-5.5	-2.5	-4.5	+0.6
014	+1.4	-1.5	-3.8	-3.1	--
015	+7.7	+5.2	+2.7	+2.4	+1.4
021	-3.5	-2.1	+0.2	-2.7	-4.5
022	-4.2	-4.7	-5.2	-2.3	-6.0
023	+1.6	+0.6	+2.8	+5.6	+6.4
024	+1.1	+1.4	-1.2	-3.8	-2.5
025	-4.2	-1.5	-1.4	+4.6	+0.1
026	+4.0	+3.7	+0.3	+4.5	+2.7
Mean	-1.0	-1.1	-1.7	-1.1	-1.0

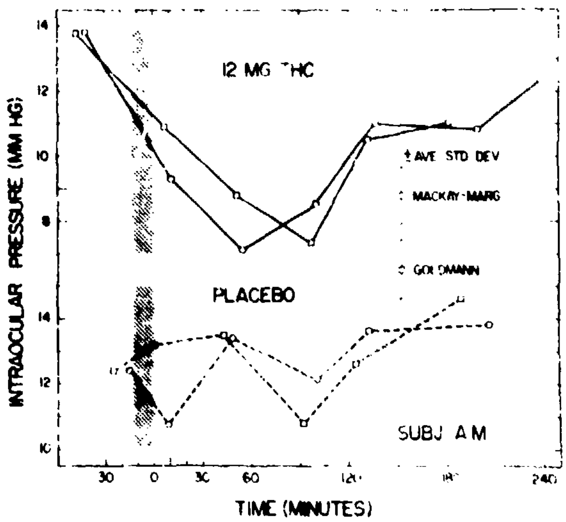

Fig. 8: Comparison of Mackay-Marg and Goldmann tonometer measurements on a subject who smoked (shaded area) marijuana and placebo.

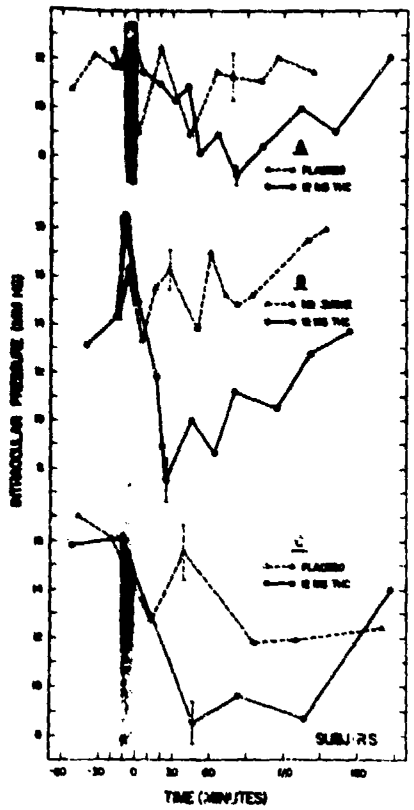

Fig. 9: Repeatability of marijuana and control effects on intraocular pressure for one subject tested over a 3 month period. Pairs of curves matched at last pre-marijuana measurement. Standard deviations indicated by vertical bar segments above or below mean pressure.

positioned vertically so that its last base-line measurement matched the last pre-marijuana measurement. Not only did the IOP drop persist with subsequent trials (A through C), but the magnitude of the drop increased from about 4.6 to 6.7 to 7.4 mm Hg. The reality of these IOP decreases with marijuana is indicated by the separation of the marijuana curves from the control curves and by the separation of the standard deviation error bars which are plotted at the test time corresponding to the lowest IOP obtained with marijuana. There is a suggestion that the IOP effect was greater with the subsequent smoking of 12 mg THC, and also that the IOP effect occurred sooner with subsequent trials.

Only 7 of 15 subjects exhibited a clear decline in IOP after marijuana. These subjects appeared less anxious, more relaxed, and more sleepy during the experiment than the subjects who had little or no IOP drop. An item analysis was performed on the responses to the Subjective Drug Effects Questionnaire (SDEQ) (cf. Section L) given to each subject at the end of the day's trials. Subjects with greater-than-mean IOP drop after marijuana reported the following symptoms significantly more often ($p < 0.03$ by the Fisher exact probability test) than did subjects with less-than-mean pressure drop: thinking seemed fuzzier, eyes felt as if closing, arms or legs felt weaker, felt more at peace with the world, felt dopey, and thoughts moved slower. Other related symptoms checked more often by subjects with above-average IOP drop were: felt pleasantly tired and sleepy ($p = 0.08$) and felt sleepier ($p = 0.12$).

Correlational analysis was performed on post-marijuana IOP change and several relevant variables (Table XIb). Two points deserve mention. First, IOP change is independent of pulse rate increment, but it is positively related to the maximum "high" rating and to the score on the 6-item SDEQ scale pertaining to peaceful relaxation and tiredness. Second, amount of marijuana experience is inversely related to IOP drop and to both subjective measures (maximum "high" rating and the 6-item SDEQ scale); marijuana experience is independent of pulse increase.

Table XIb: Ranking of Subjects by Relative Marijuana-Induced Change in Intraocular Pressure (See Column 4, Table XIa); Also Tabulated are Several Relevant Variables; Spearman Rank Correlation Coefficients Relating Pairs of These Variables are Shown at Bottom (Coefficients Larger than 0.44 and 0.62 are Significant at the 0.05 and 0.01 Levels, Respectively).

Subj. Number	IOP Change (mm Hg)	Max. Pulse Increment (Percent)	Max. High Rating (0 - 100)	SDEQ Score (0 - 6)	Marijuana Experience (Rank)
010	-5.4	39.1	80	5	13
022	-5.2	55.5	80	6	8.5
003	-4.4	55.8	88	5	12
004	-4.0	16.6	98	6	14
014	-3.8	83.3	70	4	7
008	-3.7	2.2	70	5	10
011	-2.5	22.7	85	5	11
025	-1.4	16.6	85	2	8.5
024	-1.2	9.5	50	0	1
007	-1.0	72.7	85	3	6
021	+0.2	51.5	70	3	15
026	+0.3	27.7	50	0	2
005	+1.5	43.3	80	1	3
015	+2.7	36.1	60	2	5
023	+2.8	30.0	40	0	4
Correlation Coefficients					
IOP		+0.11	+0.57	+0.83	-0.61
Pulse			+0.16	+0.15	-0.09
High				+0.68	-0.61
SDEQ					-0.78

Blood plasma concentration of Δ^9-THC has been reported by Galanter *et al.* (1972) to be highly correlated with increase in pulse rate. Dose of smoked marijuana has been found by several investigators to be related to heart rate increase (Renault *et al.*, 1971; Johnson *et al.*, 1971; Kiplinger *et al.*, 1971). Volavka *et al.* (1973) believes heart rate increase is so closely related to marijuana dose that it can be used as a bioassay of THC. To the extent that the hypothesized relationship between blood THC and pulse rate holds in our sample, IOP drop would be independent of plasma THC concentration. In any case, IOP drop in our subjects is related more to the subjective effects of smoking marijuana than to the increase in pulse rate.

Tolerance to certain marijuana effects is indicated from our results (Table XIb). Individuals who used marijuana the most tended to have little or no IOP drop ($r_s = -0.61$), and reported few drug-induced symptoms of peaceful relaxation and tiredness ($r_s = -0.78$). Subjects who used marijuana as much as 4 times per week and stayed "stoned" all day on about half the smoking occasions (Table XIb, subjects 007 and 015) exhibited little or no IOP drop; of 9 subjects with less than this usage, 7 exhibited a clear drop in IOP (Table XIb, first 7 subjects). Also the "high" ratings of the more frequent users was lower than those for less experienced users ($r_s = -0.61$) which, however, may be attributed to a scaling factor since a rating of 100 is defined as the "highest" a subject has ever felt after smoking marijuana.

In Table XIb, the subjects are ranked according to their change from baseline intraocular pressure (IOP) 80 min. after smoking 12 mg of natural THC relative to the change from baseline IOP 80 min after smoking placebo. Also tabulated are the maximum percent increase in pulse rate, the subject's maximum assessment of his "high" on a 0 to 100 scale, and the subject's score on a 6-item scale pertaining to peaceful relaxation and tiredness extracted from a 272-item check list comprising the Subjective Drug Effects Questionnaire. The last column ranks the subjects according to previous experience in smoking marijuana, rank 1 being assigned to the heaviest use. Spearman rank correlation coefficients (r_s) are read across the bottom. Coefficients larger than 0.44 and 0.62 are significant at the 0.05 and 0.01 levels, respectively. Thus the correlation (+0.11) between IOP drop and the maximum pulse increment after smoking marijuana is statistically insignificant. However, IOP drop is significantly correlated with the other 3 variables (+0.57, +0.83, and −0.61) indicating that subjects who had the larger IOP decreases after smoking marijuana tended a) to feel more "high," b) to experience more of 6 symptoms on the Subjective Drug Effects Questionnaire relating to peaceful relaxation and tiredness, and c) to be less experienced in using marijuana.

The mechanism by which marijuana reduces IOP is not understood. Green and Pederson (1973) applied THC directly to the excised ciliary body of rabbit and found a pronounced decrease in fluid secretion and an increase in ultrafiltration. Of these two changes, only the decreased secretion is consistent with the marijuana-induced IOP drop they also observed in rabbit. For man, they emphasized that, "If, however, one accepts the view that ultrafiltration is the most important process in aqueous formation . . . then one must look elsewhere for a suitable explanation."

In our study, the observed decrease in IOP in 7 of 15 subjects could have resulted from a direct effect of marijuana on the ocular fluid dynamics. On the other hand, part of the marijuana-induced IOP drop may have been an epiphenomenon or secondary effect associated with the *subjective state* created by the drug. Indeed, we found that "high" rating and the 6-item SDEQ (relaxation) score were significantly correlated with IOP drop, and we conjectured from pulse rate analysis that blood THC was probably not associated with the observed IOP decreases.

The idea that IOP can be reduced through changes in the psychophysiological state of the subject is supported by reports of IOP decline following exercise (Lempert *et al.*, 1967; Stewart *et al.*, 1970; Marcus *et al.*, 1970; Leighton and Phillips, 1970), by the successful treatment of primary glaucoma at health resorts that emphasize therapeutic exercise and mineral baths (Goncharov, 1967; Marsov, 1968; Mayachenkova, 1970), and by the clinical observation that some glaucoma patients show substantially lowered IOP after a day of hospital bed rest with no change in therapeutic drug usuage.

Social use of marijuana, particularly in relatively inexperienced users, may lead to unusually low IOP. Several of our subjects had post marijuana IOP measurements as low as 7 or 8 mm Hg. Therapeutic use of marijuana for the treatment of glaucoma seems premature considering the present state of knowledge of the drug's action (Hepler *et al.*, 1972; Shapiro, 1974). Our results suggest an indirect effect of the drug mediated through relaxation and tiredness – a psychophysiological state that can be produced by drug and nondrug means. However, heavy use of marijuana appears to prevent an IOP drop after smoking the drug. If IOP can be reduced by marijuana, alcohol, or Librium (drugs which tend to produce relaxation) as well as by nondrug means such as mild exercise, mineral baths, or hospital rest, then it seems legitimate to propose that a search for means of controlling or preventing high intraocular pressure should include the possible role of relaxation.

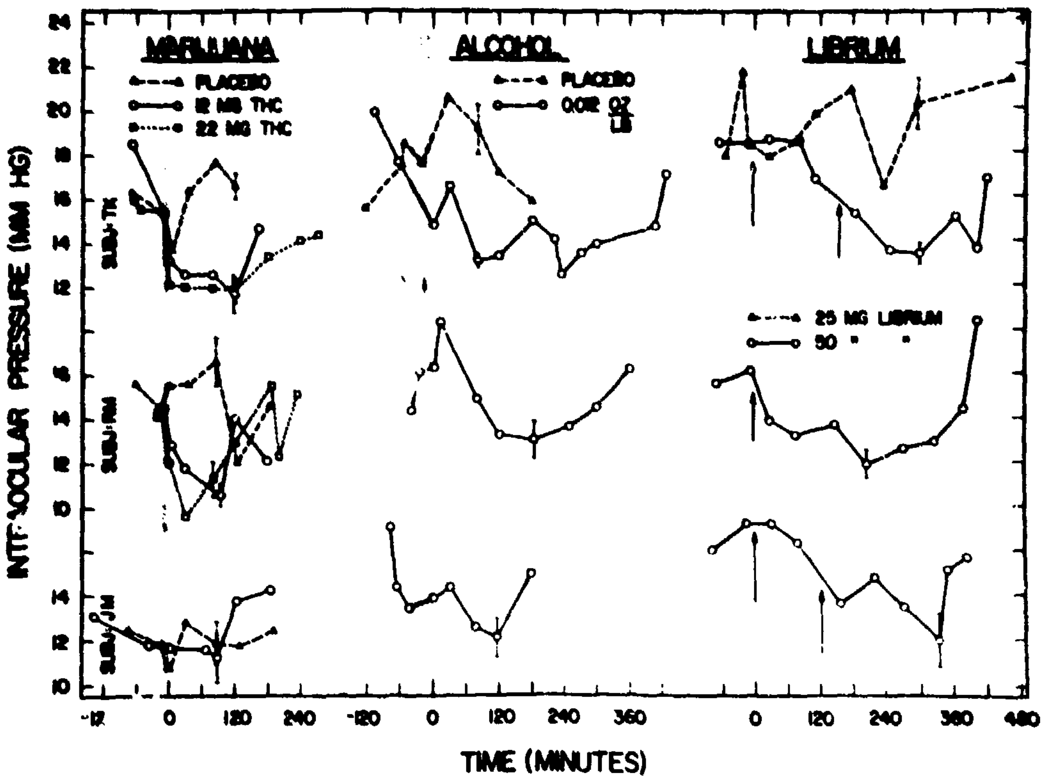

Fig. 10: Time course of intraocular pressure after marijuana, alcohol, and Librium for 3 subjects. Standard deviations indicated by vertical bar segments above or below mean points. Arrows indicate time of Librium dose.

b. Alcohol and Librium

Experiments with these drugs were undertaken in an attempt to clarify the above results obtained with marijuana. Marijuana, alcohol, and Librium are known to be relaxants. Marijuana and alcohol have diuretic effects (Ames, 1958; Houle and Grant, 1967), and marijuana, at moderate doses and Librium have anti-anxiety effects (Tart, 1971; and LeDain *et al.*, 1970). It was reasoned that if all three drugs produced similar decreases in IOP, then the IOP-reducing mechanism of marijuana might be attributed to some combination of relaxation, diuresis, and loss of anxiety.

The comparative results of our experiments on 3 subjects are illustrated in Fig. 10. Two of the subjects showed an obvious decline in IOP with marijuana, with a greater drop following 22 mg THC than following 12 mg. All three subjects had an IOP decrease with alcohol and (50 mg) Librium that lasted somewhat longer than with marijuana.

Scores on the 6-item SDEQ scale were low (1 or 2) following alcohol, and were higher (average of 3) after Librium. This result suggests that the IOP drop with alcohol may not be associated with the same psychophysiological state found with marijuana. However, the decline in IOP with Librium may be similar in mechanism to that caused by marijuana.

Since Librium is not known to be a diuretic and our experiments showed it to produce IOP decreases, it is necessary to leave open the possiblity that the IOP-decreasing effect of marijuana may in part be associated with the psychophysiological action of the drug. In addition, the diuretic action of marijuana may also contribute to the IOP decrease as occurs with alcohol ingestion (Houle and Grant, 1967).

F. Saccadic Eye Movements

1. *Procedure*

Two small spots of light were separated horizontally by 4 degrees and were viewed through +4 D lenses against a light background at 25 cm. from the lenses. The spots were illuminated alternately and the subject observed the

Table XII: Marijuana (12 mg THC) Effects on Simple Eye Movement Rhythm, Average Dwell-Time Error for Ten Fixations on Two Previously Flashing Lights (L-R-L-R); Dividing Tabulated Scores by 25 Gives Dwell-Time Error in Seconds; Minus Values Indicate Longer Dwell-Times than Previous Stimulus On-Times; Post Minus Pre-smoke Values that are Positive Indicate Increase in Saccadic Rhythm and Speeding of the Internal Clock.

	MARIJUANA			PLACEBO		
SUBJ.	Pre	Post ½ hr.	Post 1-3 hr.	Pre	Post ½ hr.	Post 1-3 hr.
001	-6.50	0	+4.25	+1.75	-6.25	-6.00
002	-3.00	+3.50	+0.50	-1.25	-0.50	+3.00
003	-1.64	-0.95	-0.80	-2.00	-5.35	+2.75
004	-5.25	-9.00	-5.20	-5.70	-6.55	-5.30
007	-7.25	-9.50	-6.65	-3.55	-8.65	-3.50
010	+3.35	+2.05	+2.31	+6.65	+6.45	+6.23
014	-0.40	+1.50	+3.35	+0.35	-1.70	+2.75
021	+4.93	+8.70	+1.80	+1.40	+2.15	+3.95
022	+5.15	-0.85	-0.75	+1.15	+4.40	+[illegible].00
023	+0.35	-0.75	+1.70	-2.10	-1.75	-1.30
024	-0.85	-1.00	-0.40	-2.35	+0.40	-1.35
025	-6.60	-6.30	-7.20	-5.55	-9.85	-5.85
026	-7.80	+1.05	-13.90	-8.85	-5.25	-4.55
Mean	-1.96	-0.89	-1.61	-1.50	-2.50	-0.17
S.D.	4.58	4.99	5.20	4.00	5.01	4.67
	ALCOHOL			PLACEBO		
004	-3.25	-4.20	-1.05			
014	+1.75	-3.35	-1.50	-0.70	+1.50	+2.40
023	+0.35	+2.50	+0.55			
Mean	-0.38	-1.68	-0.67			
	LIBRIUM-50mg.			LIBRIUM-25mg.		
004	-2.75	-7.40	-7.30			
014	-5.80	-1.80	-3.20	+0.75	-3.35	-0.40
023	+1.05	+1.50	+1.15			
Mean	-2.50	-2.57	-3.12			

lights and established a rhythm of saccadic eye movements from side to side. The lights remained on for 0.8 seconds on each side with a dark period of 0.2 seconds between one light extinguishing and the other coming on. Following 10-14 cycles of flashing lights, the flashing was stopped and the subject's task was to continue the previous saccadic eye movement rhythm. Measurement of the subject's eye movements reflects the ability of the subject to replicate the original timing of the flashing lights.

A second more complex test was introduced early in the study in an attempt to demonstrate changes which might result from marijuana intoxication. The major difference between this test and the "simple" saccadic eye movement task described above was in the pattern of light flashing. The left-right-left-right (L-R-L-R) sequence of the simple stimulus was replaced by a "L-R-R-L-R-R-L" sequence. This sequence required the subject to fixate a greater time on the right-hand light (1.25 seconds) than on the left light (0.5 seconds), both during the flashing light sequence and during the period in which self generated saccadic rhythm was required. The dark interval between right and left lights was 0.25 seconds.

The time spent on each side was measured and compared to the actual time that the eyes should have spent on that side if the subject was maintaining the original rhythm. The difference, recorded in millimeters distance on the polygraph paper, is directly convertable to time since the paper speed was 25 mm./sec. Dividing any of the individual results by 25 gives the time error in seconds. The sum of the right and left fixation time errors represents the total time error for the test. Five rightward and five leftward fixations immediately following the removal of the flashing light sequence were used for each average time error.

It was our hope that we could use this test for two purposes. First, the test allowed a check on the quality of

Table XIII: Marijuana (12 mg THC) Effects on Complex Eye Movement Rhythm. Average Dwell-Time Error for Ten Fixations on Two Previously Flashing Lights (L-R-R-L-R-R); Dividing Tabulated Scores by 25 Gives Dwell-Time Error in Seconds; Minus Values Indicate Longer Dwell-Times than Previous Stimulus On-Times; Post Minus Pre-smoke Values that are Positive Indicate Increase in Saccadic Rhythm and Speeding of the Internal Clock.

	MARIJUANA			PLACEBO		
SUBJ.	Pre	Post ½ hr.	Post 1-3 hr.	Pre.	Post ½ hr.	Post 1-3 hr.
003	+2.00	+4.15	+4.10	+2.55	+4.30	+4.25
004	-5.60	-2.70	-9.30	-8.70	-5.80	-2.20
007	-6.30	-4.25	-7.70	-0.60	-2.75	-1.95
010	+4.20	+7.05	+1.20	+10.93	+14.20	+8.60
014	-5.90	+3.50	+2.30	+0.25	-7.60	-4.90
021	+6.20	+11.30	+5.10	+5.80	+1.80	+13.50
022	+7.50	+10.50	+7.40	+2.10	+5.60	+7.60
023	+3.50	+6.70	+5.40	+0.10	-1.20	--
024	+1.80	-0.20	-2.70	-7.90	-5.90	+4.20
025	-8.50	-6.90	-7.20	-9.10	-15.50	-7.10
026	-2.70	-10.10	-6.10	+3.50	-4.30	+3.00
Mean	-0.35	+1.73	-0.67	-0.10	-1.56	+2.51
S.D.	5.62	7.10	6.09	6.30	7.89	6.50
	ALCOHOL			**PLACEBO**		
004	-3.90	-5.10	-3.90			
014	-2.50	-6.30	-3.70	+2.80	+0.80	+2.10
023	+1.80	+3.10	-0.05			
Mean	-1.53	-2.77	-2.55			
	LIBRIUM-50mg.			**LIBRIUM-25mg.**		
004	-8.60	-4.50	-9.40			
014	-5.90	-1.40	-1.40	+10.40	+7.40	+3.10
023	+0.80	+2.30	+1.80			
Mean	-4.57	-1.20	-3.00			

saccadic eye movements to ensure that the saccadic eye movement response was adequate to use in a separate objective measure of phoria (Section B, above). Second, we were looking for a simple objective test for the alterations in the internal clock that are reported to accompany marijuana smoking.

2. *Results and Comments*

a. Marijuana

Thirteen subjects were tested for simple saccadic prediction under both marijuana and placebo conditions. The results are shown in Table XII. For the group there is a mean increase in the simple saccadic rhythm after smoking marijuana while there is a mean slowing of the rhythm after smoking placebo. Further, on an individual basis, 8 of the subjects had a relatively greater increase after marijuana than after placebo. The results clearly indicate a "relative" increase in rhythm after marijuana smoking.

For complex saccadic prediction movements, as seen in Table XIII, there is a marked suggestion of increased saccadic rhythm after smoking marijuana. For the group of 11 subjects there was a mean increase of the rhythm after smoking marijuana while there was a slight mean slowing in rhythm after smoking placebo. Again this suggests a relative increase in rhythm rate associated with marijuana smoking. For complex saccadic prediction nine of eleven subjects increased their saccadic rhythm 1/2 hour after smoking marijuana while for the placebo condition five increased and six decreased their rhythm.

Our principal interest in the saccadic eye movement test was to provide an objective means of assessing changes in the internal clock. We argued that the rhythm a subject set up would reflect the internal clock, and changes in rhythm after smoking would reflect changes in the internal clock. It is apparent from our data that a subject whose internal clock is faster than real time does not necessarily have saccadic predictive eye movements that are faster

than the stimulus markers demand. In fact, of thirteen subjects who performed both the *simple* saccadic predictive eye movement task and the time production task (see next section), only four subjects showed fast or slow time clocks for both measures. By way of explanation, it could be argued that since we provide a "metric" for the eye movement rhythm in the form of blinking lights immediately prior to the self generated rhythm, there would be little time for internal clock changes to be reflected in the 5-10 seconds in which our rhythm measurements were made.

However, after smoking marijuana nine of eleven subjects showed faster *complex* predictive eye movement rhythm. Of these nine subjects, six also showed an increase in internal time clock by the time production task (see Specific Experiments, Section G). This result suggests that the complex predictive rhythm test does reflect the influence of a speeded up internal clock after smoking marijuana. Inasmuch as there was an increase in the eye movement rhythm after smoking marijuana, we might speculate that the short term memory of the metric had deteriorated. Short term memory is known to be affected by marijuana smoking. For example, Melges *et al.* (1970), using digit spans forward and backward, found that short term memory was significantly decreased after subjects took oral doses of Δ^9-THC. Implicit in our argument is the notion that giving a *simple* metric (blinking lights) normally destroys or severely reduces the test's usefulness in establishing the speed of the internal clock. However, after smoking marijuana the short term memory of the *complex* metric does appear to be affected and the internal clock is able to influence the saccadic rhythm. If this argument is correct, then the complex saccadic prediction test may represent an objective means of looking at short term memory changes.

b. Alcohol

Three subjects were given this task after drinking alcohol under the conditions outlined in the phoria test. The results are shown in Tables XII and XIII. Two subjects showed a decrease and one exhibited an increase in rhythm after drinking alcohol.

c. Librium

The drug conditions and the results for three subjects are shown in Tables XII and XIII. All three subjects showed an increase in saccadic rhythm after oral ingestion of Librium.

G. Time Estimation and Time Production

1. *Procedure and Comment*

The purpose of these tests was to detect changes in the "internal clock" following marijuana or drug treatment. An electronic timer drove a lamp which was visible to the subject. For *time estimation*, predetermined time periods of 3, 6, 12, and 24 seconds (indicated by a lighted lamp) were presented to the subject in a random order. The subject was simply requested to estimate the duration of the presentation to the nearest full second. For *time production*, the subject was asked to depress a button and hold it down for periods of 4, 7, 13, and 25 seconds. The actual time that the subject generated by pressing the button was recorded on an electronic timer in milliseconds. An over-estimation of time is consistent with an under-production of time. Both are associated with a speeding up of the internal clock with respect to real time.

Since the times used for estimation and production were constant in all experiments, the results provide an index that can be compared under different experimental conditions. The technique used in the time estimation experiments is subject to the following criticism. Subjects were given the same four time intervals to estimate each time they were tested and consequently their initial test estimates of time may have influenced the times they reported in later tests. Although subjects were not told that the test times were the same, and the order was randomized for each test, it was nevertheless possible for a subject to presume that the same times were given and to respond in the interest of consistency. Time production, however, is not subject to this criticism since the subject himself generates the time element. Consequently, it is probably a more valid test.

The time estimation and time production results were analyzed in two ways. First, the differences between the given times (either to estimate or produce) and the subject's response were summed and divided by four to give a number which reflects the total time error (plus or minus). However, this method gives an index ("time index") which is heavily biased by the longer *given* times. A second, less biased, method involves the calculation of the percent difference between the times estimated or produced prior to the drug treatment and those estimated or produced after the drug treatment. The percentage change was calculated as follows: 100 (Pre-Post)/Pre. By this analysis each of the given time periods can contribute equally to the assessment of changes in the internal time clock. The last measurement prior to the treatment and the first measurement after the treatment were used to calculate the "percentage change in time" estimation or production.

Table XIV: Marijuana (12 mg THC) Effects on Time Production. Average Error (Seconds) Combined for 4, 7, 13, and 28 Second Intervals; Minus Values Indicate Produced Time Shorter than Real Time.

	MARIJUANA			PLACEBO		
SUBJECT	Pre-Smoke	Post 1/2 hr	Post 1-3 hrs	Pre-Smoke	Post 1/2 hr	Post 1-3 hrs
001	-0.40	+0.10	+0.40	+2.30	+2.20	+2.50
002	-1.90	-1.60	-2.10	-1.05	-0.08	-0.42
003	-1.95	-3.70	-1.49	-1.27	-1.41	-0.99
004	+0.25	+0.72	+0.41	-2.48	+0.44	-0.11
007	+2.43	+0.14	-1.35	+1.03	+0.25	+1.28
010	+0.05	-1.55	-0.83	-1.70	-2.00	-0.87
014	+6.22	+1.48	+3.08	+5.C0	+9.22	+8.80
015	+0.17	+1.11	+0.90	+1.84	+1.36	+0.17
021	-0.55	+0.81	-0.01	+2.13	+3.10	+1.54
022	+0.61	-0.19	+1.20	-1.02	-0.88	-1.20
023	+3.40	-1.66	+2.92	+4.64	+5.01	+1.69
024	+0.46	+0.19	-0.42	+0.27	+0.74	-0.52
025	+1.26	+1.46	+3.15	+2.18	+0.35	+0.03
026	-1.79	-3.64	-1.21	-1.41	-2.36	-2.65
Mean	+0.59	-0.45	+0.33	+0.75	+1.14	+0.66
St. Dev.	2.23	1.72	1.75	2.36	3.06	2.71

2. *Results and Comments*

a. Marijuana

Fourteen subjects estimated and produced times prior to and following the smoking of placebo and marijuana (12 mg THC). The data were analyzed by both the "time index" and the "percentage change in time" methods. Each method yielded results consistent with a speeding up of the internal clock both in time production and time estimation.

The individual and group results for the time index method of analysis are presented in Tables XIV and XV. Table XIV gives the results for time production. For the group, the mean time production decreased after smoking marijuana and increased slightly after smoking the placebo. This reflects an increase in the internal time clock after smoking marijuana, although on an individual basis only 8 of the 14 subjects showed decreased production 1/2 hour post marijuana, and 7 decreased after placebo. Table XV gives the results for time estimation. For the group, the mean time estimation increased after smoking marijuana and decreased slightly after smoking the placebo. This also reflects an increase in the internal clock confirming the results for time production. However, the change in time estimation and production after smoking marijuana is not significantly different at the 0.05 level from the change in time estimation and production after smoking the placebo (Walsh related sample test).

Using the percentage change in the time estimation or production as a measure of the change in the time clock is an alternate method of analyzing the data. This measure has been calculated for each subject for each of the given times. The results are presented in Tables XVI and XVII. Table XVI shows that for each of the times given to

Table XV: Marijuana (12 mg THC) Effects on Time Estimation. Average Error (Seconds) Combined for 3, 6, 12, and 24 Second Intervals; Plus Values Indicate Estimated Times Longer than Real Time.

	MARIJUANA			PLACEBO		
SUBJECT	Pre-Smoke	Post 1/2 hr	Post 1-3 hrs	Pre-Smoke	Post 1/2 hr	Post 1-3 hrs
001	+0.50	0	-1.00	-1.50	-1.00	-2.50
002	+1.25	+1.25	+2.50	+0.75	-0.25	0
003	+2.00	+2.50	+3.00	+1.75	+1.25	+2.75
004	+1.50	+1.50	-0.25	+2.25	+1.50	+1.75
007	-0.75	0	-0.75	-1.00	-1.50	-1.50
010	-0.50	+1.75	+2.00	+0.25	+2.00	+1.50
014	-3.75	-0.50	-0.50	-1.50	-4.00	-4.25
015	-0.25	-0.75	-1.00	-2.00	-1.75	+0.50
021	+0.75	+0.25	+0.75	-1.75	-1.50	-1.25
022	-0.25	+1.00	+1.50	+1.00	+2.75	+0.75
023	-3.50	0	-2.50	-2.75	-3.00	-2.50
024	-1.25	-0.50	+1.00	+0.50	+0.25	+0.50
025	-1.50	-1.00	-1.25	-1.25	-0.50	+0.25
026	+1.50	+1.50	0	+1.00	0	+1.50
Mean	-0.30	+0.50	+0.25	-0.30	-0.41	-0.18
St. Dev.	1.77	1.07	1.59	1.55	1.90	1.96

produce, with the exception of the shortest time (4 seconds), there is a mean decrease in the time produced by the group after smoking marijuana, while for each given time there is a mean increase in times produced after smoking the placebo. When all times are considered together there is a mean decrease in time produced of 3.22% after smoking marijuana and a mean increase of 4.51% after smoking the placebo. Fig. 11 depicts the results graphically. Points above the line reflect increases in the internal time clock (decreases in time produced). The difference between marijuana and placebo is most clear-cut for the longest time produced (25 sec.). Table XVII shows similar changes for time estimation. A mean increase in time estimated after smoking marijuana is seen at each of the given times, while a mean decrease in time after smoking placebo is observed at all but one of the given times. Again, when all given times are considered together the results suggest an increase in the internal clock for the marijuana group. Fig. 12 depicts the results graphically. Points below the horizontal line reflect an increase in the internal clock (increases in time estimated).

Although not statistically significant, the results suggest a slight increase in the internal clock after subjects smoked marijuana. Tart (1970, 1971) and others have reported similar changes. Morrow (1944) had subjects estimate the time of 30-second, 60-second, and 5-minute intervals as well as estimate the time required to complete a simple task. He found that subjects could estimate short intervals of time quite accurately but overestimated the time required to perform a two minute task. His result suggests that the nature of the task is also important in determining changes in time perception. The clearest indications of overestimation of time are seen in studies where the subject is concurrently engaged in some activity (*Marihuana and Health*, 1971). In our tests the subject was not

Table XVI: Percentage Change in Time Production One-Half Hour after Smoking Marijuana (12 mg THC) or Placebo. Plus Values Indicate Produced Time Was Shorter after Smoking than Before, Suggesting Speeding of the Internal Clock.

	MARIJUANA				PLACEBO			
SUBJECT	Given 4 sec	Given 7 sec	Given 13 sec	Given 25 sec	Given 4 sec	Given 7 sec	Given 13 sec	Given 25 sec
001	-46.4	-7.2	+0.5	-1.0	-1.0	-10.1	+2.7	+2.7
002	-2.6	-12.7	-5.6	+1.4	-29.7	-11.2	-6.5	-6.5
003	+23.2	+13.1	+14.0	+18.6	-6.3	-2.8	+8.7	-0.7
004	-61.9	+4.9	-17.4	+8.9	-29.2	-61.6	-23.7	-26.0
007	+0.7	-0.7	+14.4	+21.0	+5.7	-10.0	+17.6	+6.7
010	+0.2	+6.8	+16.7	+14.1	+15.1	+6.6	-3.9	+3.1
014	+22.8	+25.3	+28.6	+24.7	-34.1	-52.4	-36.5	-11.8
015	+5.3	-7.9	+5.9	-15.9	+16.4	-0.5	+5.2	+1.6
021	-27.7	-6.6	-21.9	-6.2	-13.1	-3.2	-8.5	-6.0
022	-19.0	-0.4	+15.1	+6.3	-29.6	+7.1	-3.2	+0.6
023	+11.7	+34.1	+33.9	+33.0	-5.9	-7.1	-10.6	+2.9
024	-9.8	+10.0	-4.7	+4.4	-6.8	-1.5	-0.1	-5.8
025	-6.8	-2.9	-6.8	+1.9	+5.4	+3.5	+13.6	+15.5
026	+7.0	+10.9	+9.9	+23.0	+41.6	+18.1	+12.3	+0.7
Mean	-7.38	+4.76	+5.90	+9.59	-5.11	-8.94	-2.35	-1.64
St.Dev.	24.45	13.23	16.18	13.48	21.47	21.93	14.74	9.62
	Total Mean	= +3.22				= -4.51		
	St. Dev.	= 18.14				= 17.44		

asked to perform any other task during the period of time estimation or production, nor was he asked to estimate or produce long periods of time. Both the simplicity and shortness of the task may have contributed to the lack of statistical significance in the present results. Nevertheless the trend toward overestimation (and also underproduction) of time was apparent in the group results, suggesting an increase in the internal clock rate after smoking marijuana.

b. Alcohol

Time estimation and time production were measured on three subjects prior to and after drinking alcohol. The dose and conditions of the alcohol treatment were the same as in the phoria test. There is no clear trend in the results, which are shown in Tables XVIII and XIX. Subjects show both over and underestimation of time when time estimation and time production are compared before and after drinking alcohol. Only the "time index" analysis was applied to the alcohol data.

Hollister and Gillespie (1970) compared the performance of twelve subjects on a battery of tests under relatively high oral doses of alcohol and marijuana. The drug effects were similar on most tasks but different in the time perception tests. Marijuana intoxication led to overestimation of time; alcohol produced large underestimation of time. Our results are similar for the marijuana but on our limited group at low alcohol doses we do not see evidence for exaggeration of time underestimation.

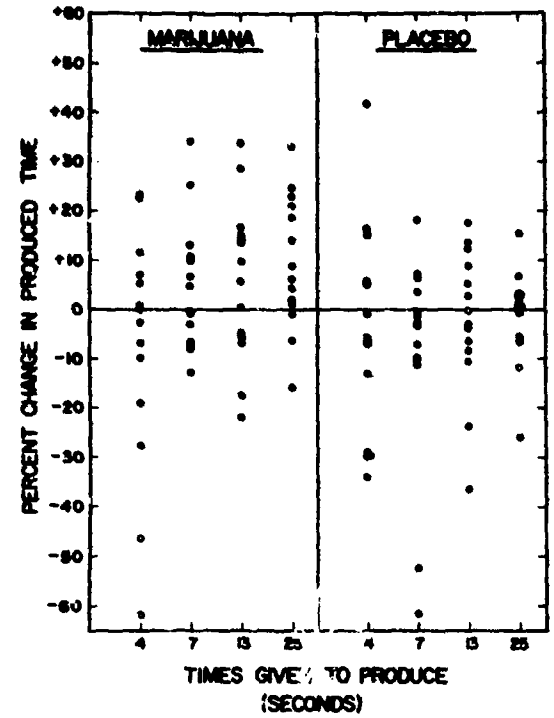

Fig. 11: Percentage change in produced time 1/2 hour after smoking marijuana or placebo. Points above horizontal line represent decreases in time produced, and thus increases in the internal clock.

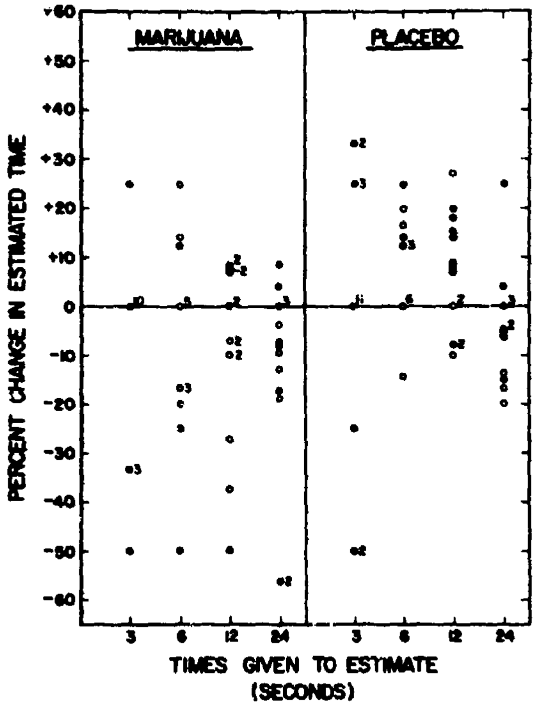

Fig. 12: Percentage change in estimated time 1/2 hour after smoking marijuana or placebo. Points below horizontal line indicate increases in estimated time, and thus increases in the internal clock.

Table XVII: Percentage Change in Time Estimation One-Half Hour After Smoking Marijuana (12 mg THC) or Placebo. Minus Values Indicate Estimated Time Was Longer after Smoking than Before, Suggesting Speeding of the Internal Clock.

	MARIJUANA				PLACEBO			
SUBJECT	Given 3 sec	Given 6 sec	Given 12 sec	Given 24 sec	Given 3 sec	Given 6 sec	Given 12 sec	Given 24 sec
001	0	0	+7.7	+4.0	0	0	-10.0	-4.8
002	-33.3	0	+7.1	-3.8	+25.0	+14.3	+8.3	+4.0
003	0	+12.5	-7.1	-7.4	0	+12.5	+7.1	0
004	+25.0	+25.0	-7.1	-8.0	0	+12.5	+14.3	0
007	0	0	+8.3	-19.0	+33.3	0	+18.2	-4.8
010	-33.3	-16.7	-27.3	-17.4	0	-14.3	-7.7	-16.7
014	-50.0	-25.0	-50.0	-56.3	+33.3	+20.0	+27.3	+25.0
015	0	-16.7	+8.3	+8.7	0	0	0	-5.3
021	C	+14.3	+7.7	0	-50.0	0	+9.1	-5.0
022	-33.3	-16.7	0	-13.0	-25.0	0	-7.7	-20.0
023	0	-50.0	-37.5	-56.3	-50.0	+16.7	+20.0	-6.3
024	0	0	-10.0	-9.5	+25.0	+25.0	+7.7	13.6
025	0	-20.0	-10.0	0	0	0	0	-15.0
026	0	0	0	0	+25.0	+12.5	+15.4	0
Mean	-8.92	-6.66	-7.85	-12.71	+1.19	+7.09	+7.29	-4.46
St.Dev.	20.26	19.07	18.39	20.05	27.31	10.67	11.28	11.06
	Total Mean		= -9.04			=+2.77		
	St. Dev.		= 19.06			=16.91		

c. Librium

Three subjects were given Librium under the same conditions as those used in the glare recovery tests. Time estimation and time production were measured in each subject and analyzed by the "time index" method. The results are presented in Tables XVIII and XIX. No clear trends emerge, there being increases and decreases in time estimation in different subjects.

H. Sinusoidal Pursuit Eye Movments

1. *Procedure*

A spot of light presented on an oscilloscope face was moved back and forth horizontally through an angle of 19 degrees, in a sinusoidal motion, while the subject viewed the spot from a distance of 11 inches. Frequency of sinusoidal oscillation increased regularly and automatically from one-half cycle per second (Hertz) to three cycles per second (Hertz) over a period of 28 seconds. The highest frequency at which the subject could accurately follow the sinusoidally oscillating target was recorded as the end point of the test.

In addition to the above stimulus conditions, the target was presented against the lighted grid of the oscilloscope ("grid present" condition). Moskowitz *et al.* (1972) have suggested that divided attention tasks may be sensitive measures of drug use. In the "grid present" condition it was our hope that we had created a type of divided

Table XVIII: Alcohol (0.012 oz/lb) or Librium (25 or 50 mg) Effects on Time Production. Average Error (Seconds) Combined for 4, 7, 13, and 25 Second Intervals; Minus Values Indicate Produced Time Shorter Than Real Time.

	ALCOHOL			PLACEBO		
SUBJECT	Pre-Ingest.	Post 1/2 hr	Post 1-3 hrs	Pre-Ingest.	Post 1/2 hr	Post 1-3 hrs
004	+3.68	+5.08	+2.98			
014	+5.72	+4.20	+3.53	+4.04	+5.10	+5.97
023	+3.17	+4.53	+4.34			
Mean	+4.19	+4.60	+3.62			
St. Dev.	1.35	0.44	0.68			
	LIBRIUM - 50 mg.			LIBRIUM - 25 mg.		
004	+5.2	+2.93	+4.6			
014	+5.22	+7.49	+7.3	+6.4	+7.8	+6.95
023	+0.88	+0.90	+0.6			
Mean	+3.77	+3.77	+3.99			
St. Dev.	2.50	3.37	3.66			

Table XIX: Alcohol (0.012 oz/lb) or Librium (25 or 50 mg) Effects on Time Estimation. Average Error (Seconds) Combined for 3, 6, 12, and 24 Second Intervals; Plus Values Indicate Estimated Time Longer than Real Time.

	ALCOHOL			PLACEBO		
SUBJECT	Pre-Ingest.	Post 1/2 hr	Post 1-3 hrs	Pre-Ingest.	Post 1/2 hr	Post 1-3 hrs
004	-3.00	-2.75	-2.00			
014	-2.00	-2.25	-2.00	-2.00	-2.00	-1.25
023	-2.00	-2.75	-4.00			
Mean	-2.33	-2.58	-2.67			
St. Dev.	0.58	0.29	1.15			
	LIBRIUM - 50 mg.			LIBRIUM 25 mg.		
004	-2.00	-0.75	-0.50			
014	-2.00	-3.25	-0.30	-3.50	-3.75	-3.75
023	-2.75	-1.25	-1.00			
Mean	-2.25	-1.75	-1.50			
St. Dev.	0.43	1.32	1.32			

Table XX: Marijuana (12 mg THC) Effects on Maximum Frequency (Hertz) of Smooth Ocular Following Movements for Sinusoidal Motion of Spot over Nineteen Degree Extent, With and Without Reference Grid in the Field.

	MARIJUANA (12 mg. THC)						PLACEBO					
	No Grid			Grid Present			No Grid			Grid Present		
Subject	Pre Smoke	Post 1/2 hr	Post 1-3 hr	Pre Smoke	Post 1/2 hr	Post 1-3 hr	Pre Smoke	Post 1/2 hr	Post 1-3 hr	Pre Smoke	Post 1/2 hr	Post 1-3 hr
001	2.12	1.90	2.01	--	--	--	2.16	1.82	2.07	--	--	--
002	2.22	2.26	2.63	--	--	--	2.41	2.28	2.21	--	--	--
003	2.07	1.93	1.90	2.07	1.92	1.65	2.17	2.31	2.11	1.90	2.15	2.12
004	2.20	2.25	2.05	2.60	2.80	1.90	2.35	2.17	2.15	1.94	2.10	2.15
007	1.68	1.85	1.83	1.63	1.64	1.81	1.88	1.80	1.73	1.80	1.50	1.50
010	1.67	1.45	1.37	1.55	1.45	1.35	1.57	1.65	1.76	1.55	1.71	1.38
014	2.20	2.12	2.12	2.05	2.10	2.25	2.24	2.07	2.15	1.91	1.78	1.82
015	1.30	1.10	1.32	1.60	1.10	1.30	1.16	1.58	1.30	1.60	1.10	1.25
021	1.85	1.70	1.82	1.65	1.10	1.50	1.93	[illegible]	1.70	2.05	1.55	1.82
022	2.06	2.20	2.23	1.90	2.00	1.86	2.20	1.97	2.11	1.90	1.92	1.82
023	1.67	2.29	2.11	1.72	1.26	2.02	1.91	2.06	1.96	1.88	1.80	1.78
024	2.02	2.05	2.23	2.18	2.10	1.90	2.32	2.58	2.55	2.50	2.30	2.58
025	1.44	1.42	1.62	1.34	1.56	1.50	1.47	1.58	1.64	1.54	1.50	1.49
026	1.67	1.59	1.85	1.82	1.31	1.98	1.45	1.36	1.72	1.40	1.10	1.09
Mean	1.87	1.86	1.93	1.84	1.69	1.75	1.94	1.93	1.94	1.83	1.71	1.73
St. Dev.	0.30	0.37	0.35	0.34	0.51	0.29	0.39	0.34	0.32	0.29	0.38	0.42

attention eye movement task.

The performance on both tasks was scored in an identical fashion. The end-point performance was expressed as a frequency of stimulus oscillation in Hertz.

It was extremely difficult to quantify the performance on this test. Subjects often intermittently failed to follow the target only to regain good eye tracking at higher frequencies. After extensive qualitative examination of the data, certain rules for scoring were instituted as follows:

a. An error is scored when the eye does not follow the stimulus with at least one half the amplitude of the immediately preceding normal amplitude eye movements.

b. The end point of the test occurs when an error is not followed by at least 4 cycles of normal eye movements.

2. *Results and Comments*

a. Marijuana

Fourteen subjects were examined under both placebo and marijuana conditions. Twelve of the subjects were tested for the "grid present" and the "no grid" conditions. The remaining two subjects were tested for the "no grid" condition alone. One or two tests were given to establish pre-smoking performance. Where two tests were given, the average was calculated to represent the pre-smoking performance. Each test involved two trials for the "no grid" condition and one trial for the "grid present" condition. The results are shown in Table XX.

In the "no grid" condition there was no change in eye tracking performance for the group following either placebo or marijuana smoking. Fig. 13 depicts each subject's change in pursuit tracking following marijuana (ordinate) plotted against his change after placebo (abscissa), with no grid present. Points above the horizontal line represent decreased tracking performance following marijuana; points right of the vertical line represent decreased performance after placebo. Considering only the direction of shift for each subject it can be seen that 8 of the 14 subjects showed a decreased performance after marijuana; there were also 8 decreased performances after placebo. A "relative performance" change is obtained for each subject by using his performance after placebo as the standard for his marijuana effect, rather than using his marijuana result. The diagonal line of Fig. 13 separates the 6 subjects with relative decreases with marijuana compared with placebo (points above diagonal) from the 8 subjects with relative increases with marijuana (below diagonal).

For the "grid present" condition there is no statistically significant change in eye tracking performance after smoking placebo or marijuana (Table XX). Under both conditions, however, there is a suggestion that tracking performance decreased slightly after smoking. In Fig. 14 each subject's change in pursuit tracking following marijuana (ordinate) is plotted against his change following placebo (abscissa), with a grid present. Points above the horizontal line represent decreased performance after marijuana (7 of 12 subjects); points to the right of the vertical line represent decreased performance after placebo (8 subjects). Again, the comparison of placebo and marijuana is most significant when each subject's marijuana performance is compared to his placebo performance: the relative performance with marijuana decreased in 5 subjects, whose points are above the diagonal line; 6 subjects showed a relative increase after marijuana, as indicated by points below the diagonal.

It is apparent that there was little or no change in eye tracking performance for the group as a result of marijuana smoking. However this conclusion is offered with a great deal of caution. It is extremely difficult to establish an effective metric for the eye tracking performance in this task. The above conclusions were drawn from our attempts to measure the highest frequency at which the subject could still accurately follow. This frequency was determined by two relatively arbitrary rules designed to quantify the "breakdown" frequency as indicated by visual inspection of the records. There are, of course, a number of other methods for looking at eye tracking performance including phase error, amplitude loss, and various combinations of these.

So-called "hand-eye" tracking has been shown to deteriorate after marijuana smoking (Manno *et al.*, 1970). Smooth following eye movements might be expected to be altered by marijuana smoking since they involve both motor tracking by the eyes and sensory acknowledgement of the visual stimulus. In our study, subtle changes in eye movement tracking may have gone undetected.

The sinusoidal eye movement task is of great interest in the comparison of alcohol and marijuana effects. The next section of this report indicates that relatively clear changes in eye movement tracking performance occurred following low or moderate doses of alcohol.

b. Alcohol

Five subjects were tested for changes in sinusoidal eye tracking performance after alcohol intake. One of the subjects was also tested for the placebo alcohol condition. The alcohol conditions were the same as those described for the phoria test.

Tests were made prior to and following the intake of alcohol. At least two measures were determined following the alcohol drinking; one at approximately 60 minutes (35-80 minutes) and one at 150 minutes (120-210 minutes) Both "grid present" and "no grid" tasks were given to three of the subjects. Their blood alcohol levels were approximately 0.07% at about 30 minutes after drinking. The remaining two subjects were given two doses of alcohol and their tracking performance on the "no grid" task was followed at frequent intervals. Their results are illustrated in Fig. 15a. Both subjects showed a clear deterioration in eye tracking performance after drinking alcohol. The actual record of one of these subjects is seen in Fig. 15b.

The individual results as well as the means and standard deviations for the group are given in Table XXI. All subjects decreased their tracking performance after drinking alcohol. This was true both for the "grid present" and "no grid" conditions. The reduced tracking performance after the subjects drank alcohol was more pronounced for the "grid present" task suggesting that the complex visual field made it more difficult for the eyes to follow the oscillating target. The 0.31 Hertz decrease (2.24 to 1.93 Hz) in sinusoidal tracking performance one hour following alcohol intoxication is statistically significant at the 0.06 level for the "no grid" condition. For the "grid present" condition the drop is even larger (0.48 Hertz). Fig. 16 shows the results for the three subjects who performed the task for the "grid present" condition.

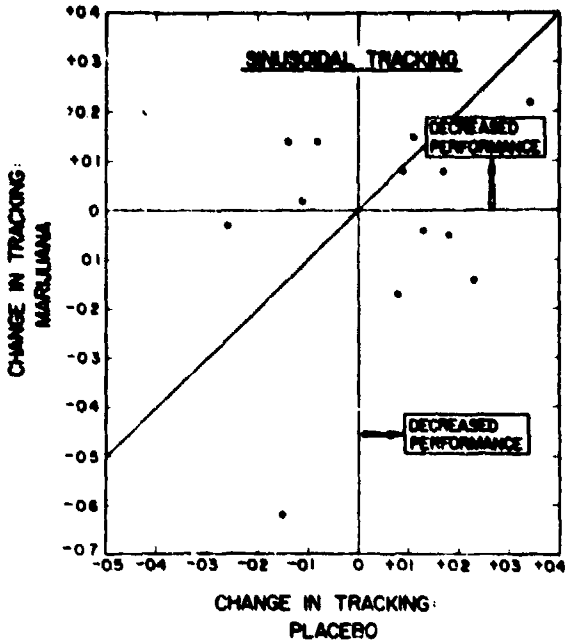

Fig. 13: Marijuana and placebo effects (1/2 hour after smoking) on change in maximum frequency (Hz) of horizontal ocular following movements for sinusoidally moving spot without reference grid in field. Points above diagonal indicate greater decrease in tracking after marijuana than placebo.

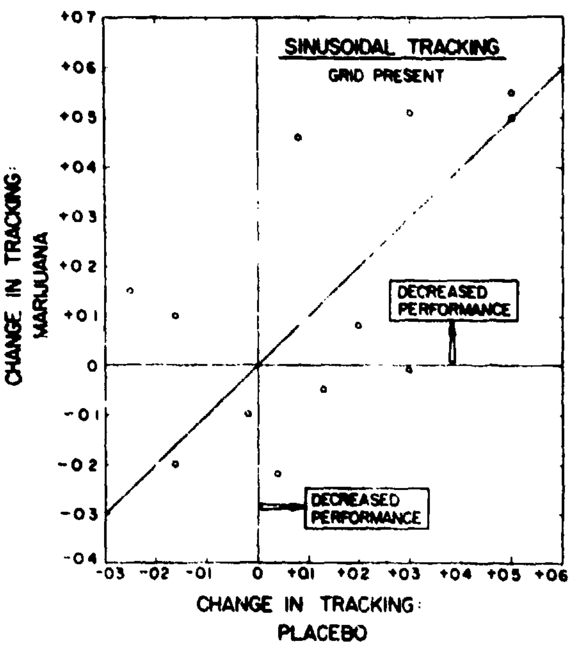

Fig. 14: Marijuana and placebo effects (1/2 hour after smoking) on change in maximum frequency (Hz) of horizontal ocular following movements for sinusoidally moving spot with reference grid in field. Points above the diagonal indicate greater decreases in tracking performance after marijuana than placebo.

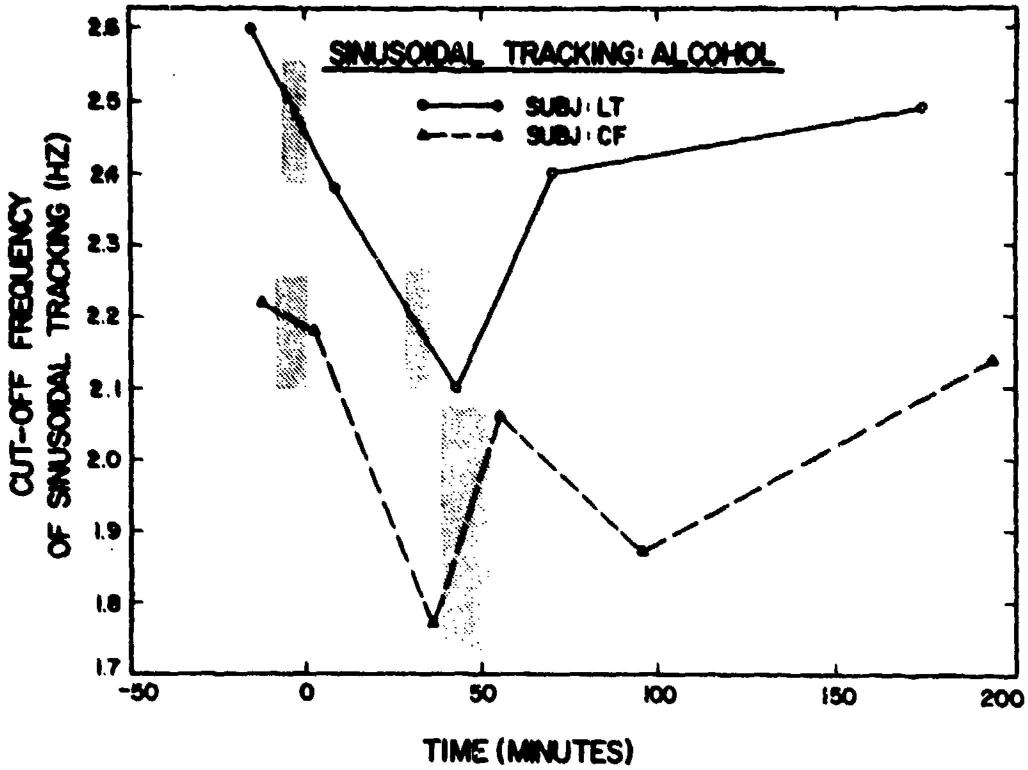

Fig. 15a: Alcohol effects on time course of maximum frequency of horizontal ocular following movements for sinusoidally moving spot of increasing frequency, grid not present in field. Shaded areas represent drinking periods (first: 4 oz, 80 proof; second: 2 oz, 80 proof).

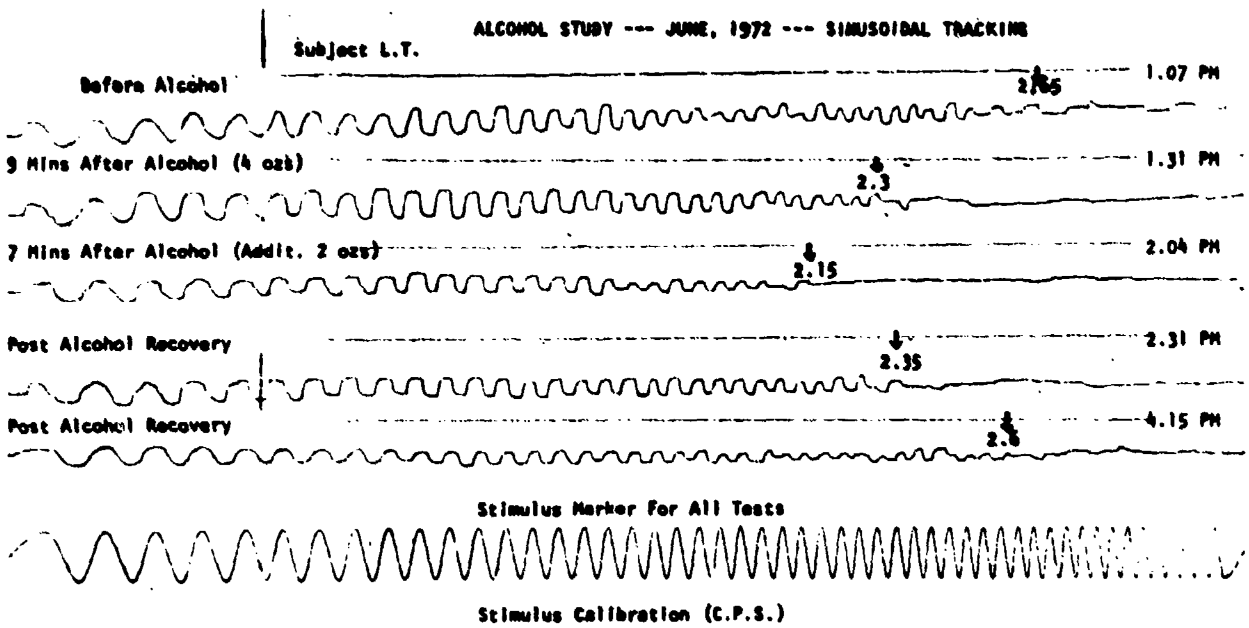

Fig. 15b: Electro-oculographic records (upper traces) showing alcohol effects on one subject's maximum pursuit tracking frequency (arrows and cutoff frequencies in Hertz) for increasing sinusoidal velocity of horizontally moving spot (bottom trace).

Table XXI: Alcohol (0.012 oz/lb) Effects on Maximum Frequency (Hertz) of Smooth Ocular Following Movements for Sinusoidal Motion of Spot over Nineteen Degree Extent, With and Without Reference Grid in the Field.

	ALCOHOL						PLACEBO					
	No Grid			Grid Present			No Grid			Grid Present		
Subject	Pre Alcohol	Post 1 hr	Post 2 1/2 hrs	Pre Alcohol	Post 1 hr	Post 2 1/2 hrs	Pre Alcohol	Post 1 hr	Post 2 1/2 hrs	Pre Alcohol	Post 1 hr	Post 2 1/2 hrs
004	2.25	2.03	2.06	2.63	1.70	1.92	--	--	--	--	--	--
012	2.60	2.10	2.49	--	--	--	--	--	--	--	--	--
013	2.22	1.77	1.87	--	--	--	--	--	--	--	--	--
014	2.05	1.82	1.91	1.90	1.70	1.92	2.17	2.04	2.00	1.84	1.92	1.76
023	2.07	1.95	1.84	2.02	1.70	1.77						
Mean	2.24	1.93	2.03	2.18	1.70	1.87						
St. Dev.	0.22	0.14	0.27	0.39	0	0.09						

These interesting results should be tested on a larger group of subjects, particularly under conditions of divided attention. The apparent difference between the alcohol and marijuana results may help differentiate between the effects of the two drugs.

c. Librium

Sinusoidal eye tracking was measured on three subjects before and after oral ingestion of 50 mg of Librium. One of the subjects was given 25 mg of Librium on a second experimental day. The individual results are presented in Table XXII along with the means and standard deviations for both the "grid present" and "no grid" conditions. The eye movement tracking performance of all three subjects deteriorated within 1 hour after taking the Librium when given the "grid present" task condition (including the low dose condition given to one subject). However, for the "no grid" condition two of the three subjects showed an improvement. There appears to be a group change for the "grid present" condition but not for the "no grid" condition. The significance of this result cannot be adequately assessed on such a small group. Future work in this area should be directed toward a larger group of subjects where the task condition approaches a divided attention format.

I. Pupil Diameter, Conjunctival Injection, Lid Edema

1. *Procedure and Comment*

Conjunctival injection ("reddening") is one of the most consistent signs associated with marijuana smoking (Tart, 1969). It apparently is not due to direct irritation from the smoke since it also occurs with oral doses of marijuana (*Marihuana: A Signal of Misunderstanding*, 1972). The degree of injection seems to be related to the dose level, being greater for larger doses, and seems to be greater 15 minutes after smoking than at 90 minutes after smoking (Weil *et al.*, 1968). However, its time course is much longer than that of pulse rate increment.

Pupil diameter changes have been variously reported in the literature. Early reports (Mayer-Gross *et al.*, 1960) suggested that the pupil enlarges after smoking marijuana. Other studies have suggested that pupil size does not change (Tart, 1969). More recent studies report that a slight decrease in pupil diameter follows marijuana smoking (Hepler *et al.*, 1972).

Color slides were obtained by photographing the left eye. From the projected slides the degree of conjunctival injection, pupillary diameter, and lid edema were qualitatively assessed.

2. *Results*

As pointed out in the Introduction, the major reasons for looking at the conjunctival injection, pupil diameter, and lid edema were to confirm previous reports on these functions and to aid in the possible interpretation of reports on these functions and to aid in the possible interpretation of results found in our study. We have confirmed

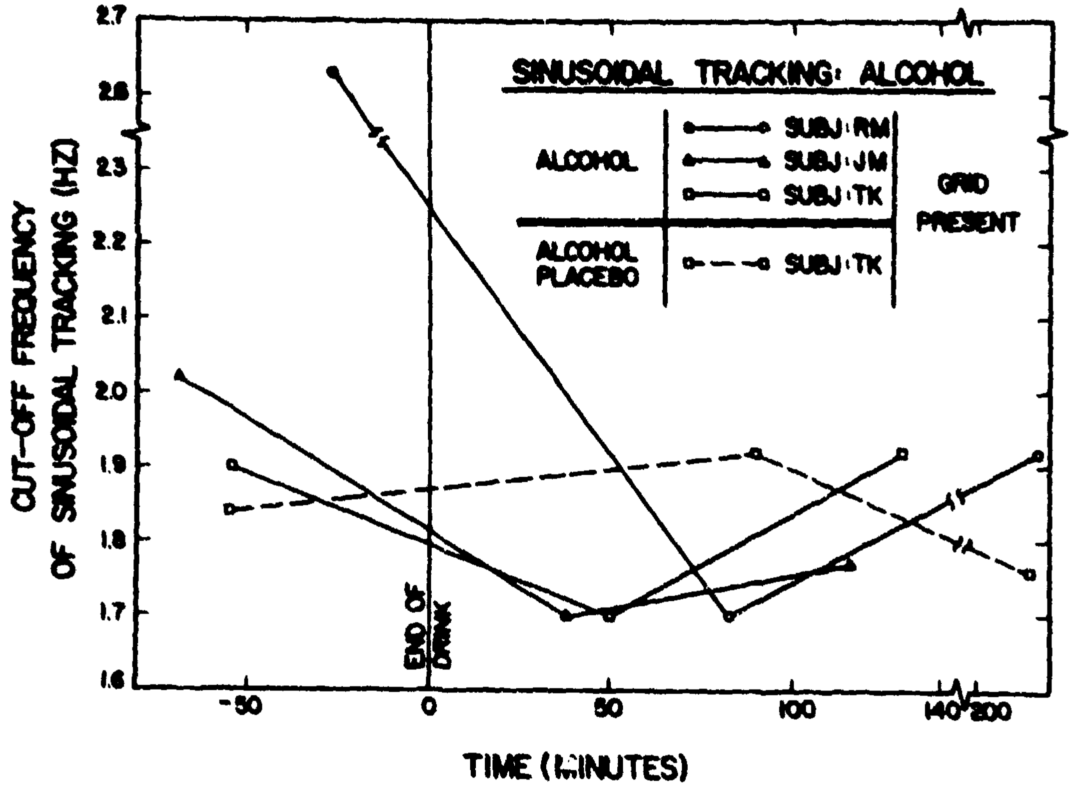

Fig. 16: Alcohol effects on time course of maximum pursuit tracking frequency for sinusoidally moving spot of increasing frequency. Grid present in field.

Table XXII: Librium (25 and 50 mg) Effects on Maximum Frequency (Hertz) of Smooth Ocular Following Movements for Sinusoidal Motion of Spot over Nineteen Degree Extent, With and Without Reference Grid in the Field.

	LIBRIUM 50 mg.						LIBRIUM 25 mg.					
	No Grid			Grid Present			No Grid			Grid Present		
Subject	Pre Librium	Post 1 hr	Post 2 1/2 hrs	Pre Librium	Post 1 hr	Post 2 1/2 hrs	Pre Librium	Post 1 hr	Post 2 1/2 hrs	Pre Librium	Post 1 hr	Post 2 1/2 hrs
004	2.37	2.49	2.22	2.52	2.20	2.18	--	--	--	--	--	--
014	2.08	1.92	1.98	2.00	1.88	2.19	1.94	1.96	1.82	1.86	1.65	1.70
023	1.85	2.09	2.39	2.04	1.55	1.92	--	--	--	--	--	--
Mean	2.10	2.17	2.20	2.19	1.88	2.19						
St. Dev.	0.26	0.29	0.21	0.29	0.33	0.15						

the conjunctival injection which follows marijuana smoking, and our measurements of pupil size suggest that a very slight pupil constriction occurs, but not invariably. Our tentative results are consistent with the recent report of slight pupillary constriction (Hepler *et al.*, 1972) just after smoking marijuana.

A number of subjects showed a ptosis condition ("lid droop") following marijuana smoking and our film records suggest that this is primarily due to lid edema rather than a change in the muscle innervation to the lids.

Table XXIII: Radial Pulse Rate (Beats/Minute) after Smoking Marijuana (12 mg THC) or Placebo.

	MARIJUANA						PLACEBO					
SUBJECT	Pre-5 min	Post 5 min	Post 30 min	Post 80 min	Post 120 min	Post 180 min	Pre-5 min	Post 5 min	Post 30 min	Post 80 min	Post 120 min	Post 180 min
003	77	120	102	68	64	62	62	78	78	70	70	66
004	72	84	80	-	72	76	68	68	72	68	76	72
005	60	86	82	70	62	62	68	72	60	60	64	64
007	88	152	112	-	104	108	72	-	72	76	-	68
008	90	92	90	72	70	82	62	62	66	68	64	-
010	92	128	120	104	116	92	84	90	84	88	84	80
011	88	108	96	78	80	86	86	84	84	78	80	74
014	72	132	108	82	84	-	68	68	68	72	68	-
015	72	98	84	80	-	76	80	96	80	80	68	-
021	66	100	76	76	79	76	56	60	56	-	-	64
022	108	168	144	116	104	-	92	88	88	88	108	82
023	80	104	88	76	88	-	68	68	72	88	88	80
024	84	92	84	78	76	74	92	100	80	78	80	80
025	72	84	82	68	68	-	68	64	64	-	64	64
026	72	92	90	72	72	-	76	76	76	68	72	-
Mean	79.5	109.3	95.9	80.0	81.4	79.4	73.5	76.7	73.3	75.5	76.0	72.2
Diff.		+29.8	+16.4	+0.5	+1.9	-0.1		+3.2	-0.2	+2.0	+2.5	-1.3
% Diff.		+37.4	+20.6	+0.6	+2.3	-0.1		+4.3	-0.2	+2.7	+3.4	-1.7
St.Dev.	12.2	25.7	18.5	14.2	16.3	13.7	11.1	13.0	9.3	8.9	12.4	7.3

J. Pulse Rate

1. *Procedure*

The pulse rate was monitored during all experiments. At least three determinations of pulse rate were made prior to the drug treatment and a regular series of measurements (about ten) was obtained following the drug treatment. For about one half of the experiments radial pulse rate was determined by hand. For the remaining experiments pulse was determined using skin electrodes as described in the General Experimental Methods. For five of the subjects, pulse rate was continuously monitored prior to, during, and immediately following the marijuana and placebo smoking.

2. *Results and Comments*

a. Marijuana

Pulse rate was monitored for both placebo and marijuana smoking conditions for 15 subjects. All subjects showed an increase in pulse rate after smoking marijuana. The mean increase was 30 beats/minute five minutes after smoking and 16 beats/minute 30 minutes after smoking. The mean increase five minutes after smoking placebo was 3 beats/minute, an insignificant change. The individual results are shown in Table XXIII. The middle curves of Fig. 7 show the mean pulse rate during the experiment for both placebo and marijuana conditions. Although this figure does not allow resolution of the peak pulse rate, Table XXIII indicates that it is clearly reached before the post 30 minutes time. By 80 minutes the mean pulse rate is the same as that prior to smoking. On the other hand there is no significant increase in pulse rate after smoking the placebo.

The most consistent physiological sign after marijuana smoking is an increased pulse rate (*Maribuana: A Signal of Misunderstanding*, 1972). Marijuana does not appear to act directly on the heart (Manno *et al.*, 1970). Heart rate increase can be prevented by pre-treatment with propranol, a beta-sympathetic nervous system blocking agent (Kiplinger *et al.*, 1971). Renault *et al.* (1971) have also suggested that marijuana may act by altering the normal autonomic tone. These authors found that the heart rates for high doses of marijuana were of the same order as is found in the absence of vagal tone, supporting the notion that marijuana alters autonomic tone. In the same experiments Renault *et al.* found linear dose-effect curves which were repeatable in the same subject and which showed no differences between experienced and inexperienced smokers. There were, however, fairly large differences in the magnitude of the effect from individual to individual. Moskowitz *et al* (1972) measured heart rate on twelve males between the ages of 21 and 29 before and after smoking placebo and marijuana (200 μg Δ^9THC/kg body wt.). They found the average increase in heart rate to be 46.5 beats after marijuana smoking and 8.5 beats after placebo smoking. Weil *et al.* (1968) have reported that the observable effects of marijuana were at a maximum 15 minutes after smoking while others have suggested that maximal observable effects are some time later. Indeed, it has been suggested that heart rate reaches a peak about 15 to 20 minutes after finishing smoking and returns to normal at about one to one and one-half hours after smoking (*Maribuana: A Signal of Misunderstanding*, 1972). This reported time may reflect the fact that many researchers (Renault *et al.*, 1971; Moskowitz, 1972; Weil *et al.*, 1968) either did not measure the pulse rate until at least 10 minutes after the completion of smoking or did not report the times at which pulse rate was measured. Galanter *et al.* (1972) have shown a close relationship between pulse increment and plasma concentration of Δ^9THC both being maximal approximately 15 minutes after smoking, the first time at which measurements were made.

In view of the consistent reports which suggest that the increase in pulse rate is sufficiently dose-related and reproducible for use as a quantitative indication of the THC dose for a given individual (*Maribuana and Health*, 1971), it seems important to establish the time course of pulse rate changes more precisely during and after smoking marijuana. Perez-Reyes *et al.* (1972) showed that intravenous injection of a special preparation of either Δ^9THC or its 11-hydroxylated metabolite (11-OH-Δ^9THC) produced an increase in pulse rate immediately after intravenous injection began. They included heart rate measurements approximately 2, 7, 12, 17, and 22 minutes following the completion of intravenous injection. The heart rates were at a maximum at 7, 12, and 17 minutes; it is not clear where in this range the peak occurred. It is also unclear how this study relates to the more normal route of ingestion, namely smoking.

In our study we continuously monitored and recorded pulse rate with Beckman skin electrodes before, during, and following marijuana and placebo smoking. A total of 5 subjects were monitored for the marijuana condition, two of these were also monitored for the placebo condition. The results for one subject smoking marijuana and one subject smoking placebo reflect the changes which were fairly typical for the group.

Fig. 17 shows the results for a subject smoking marijuana. The time course for this subject is similar to that followed by the other four subjects, with the exception of the initial pulse rate being unusually high prior to smoking and the maximum change being larger than we observed in other subjects. The important points to be noted are: (1) The pulse rate increased immediately after the subject began smoking marijuana and increased continuously during the smoking period. (2) At the time the subject completed smoking the marijuana (8 minutes elapsed time in this case), the pulse rate was very close to its peak. (3) The pulse rate returned to normal after about 60 minutes. All 5 of the subjects reached the peak increase in pulse rate within 5 minutes *after* smoking marijuana and returned to their pre-smoking levels between 50 and 90 minutes after smoking.

Fig. 18 illustrates the results for a subject smoking placebo. It can be seen that the small pulse increase that occurred is almost entirely confined to the period during smoking. A second subject showed a larger increase after placebo smoking, reaching a peak during the smoking. His pulse had returned to normal between 7 and 19 minutes after smoking.

These results show that the peak pulse increase occurs within 5 minutes of the completion of marijuana smoking for all 5 subjects, and not 15 to 20 minutes after smoking as suggested by previous reports. This result is significant, since there is evidence that pulse rate reflects the THC blood plasma level (Galanter *et al.*, 1972).

b. Alcohol

The alcohol treatment was described in the section (B) for the phoria test. In all 5 subjects who participated in alcohol experiments there was no change in pulse rate following alcohol ingestion.

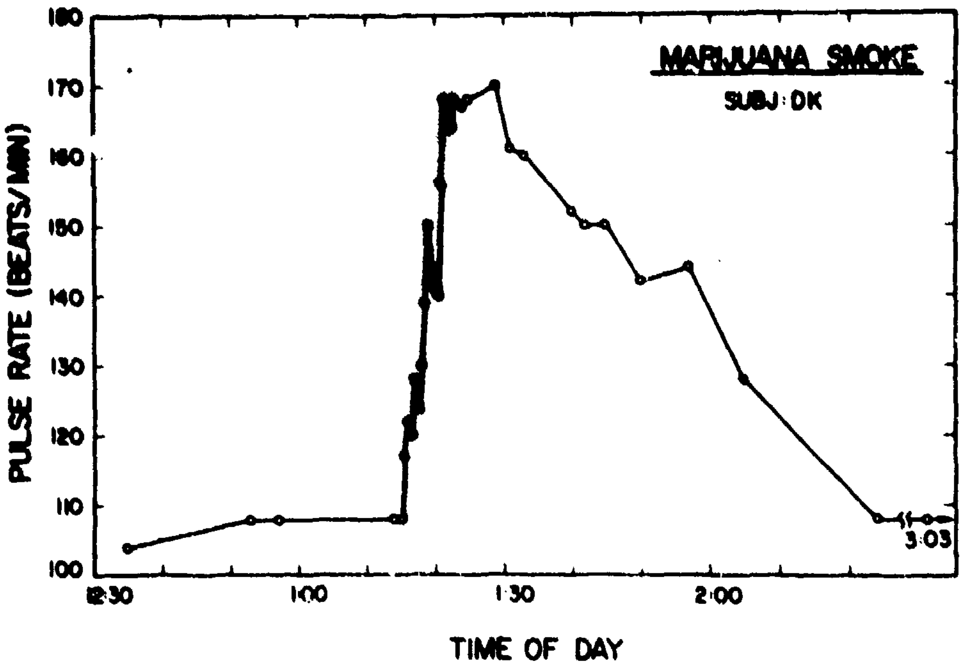

Fig. 17: Time course of pulse rate before, during (shaded area), and after smoking marijuana.

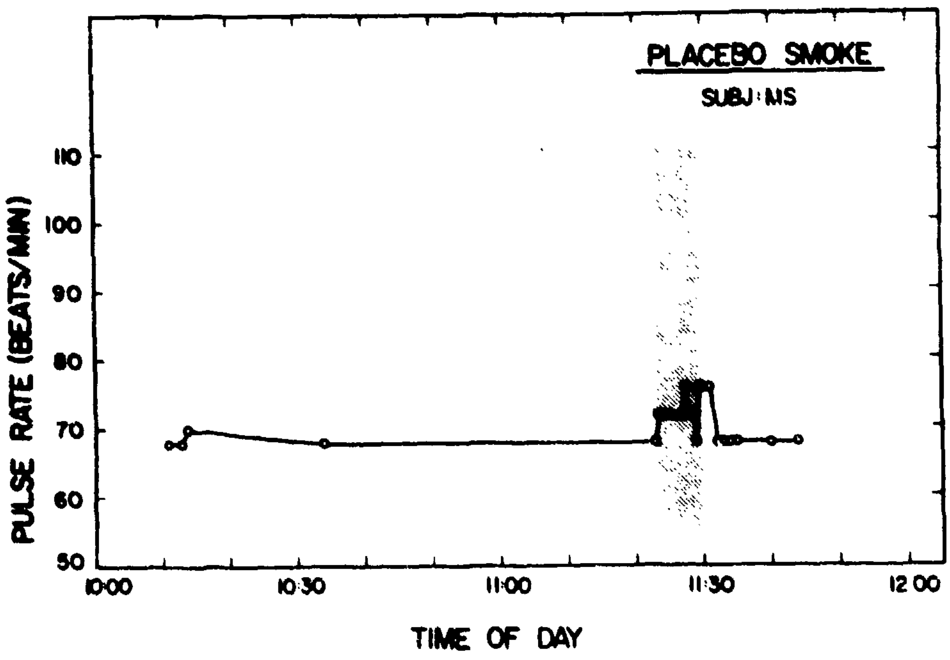

Fig. 18: Time course of pulse rate before, during (shaded area), and after smoking placebo.

c. Librium

Three subjects were given 50 mg of Librium (two 25 mg doses for each of 2 subjects and one 50 mg dose for the third). One subject was also given a single 25 mg dose of Librium. The pulse rate was unaltered by any of the treatments.

K. High Rating

1. *Procedure and Comment*

Most studies on the effects of marijuana smoking on performance attempt to get a subjective estimate of the subject's "high" during the experiment. In our study each subject was periodically asked to assess his "high" on a 0 to 100 scale, where 0 meant "not high at all" and 100 was the "highest" a subject had ever been on any previous occasion after smoking marijuana. The rating is therefore influenced by each subject's previous experience. "High" ratings have been used by a number of investigators (Weil *et al.*, 1968; Caldwell *et al.*, 1969; Crancer *et al.*, 1969; Rodin *et al.*, 1970; and Isbell *et al.*, 1967). The peak "high" is generally considered to occur after the peak pulse rate and to decline more slowly. Galanter *et al.* (1972) showed that the subjective "high" peaked at about one hour after smoking marijuana and declined very slowly.

2. *Results*

a. Marijuana

The "high" rating was determined on 15 subjects at regular intervals after smoking marijuana. A total of about 10 assessments were made on each subject. Table XXIV shows the individual "high" ratings at selected times after smoking marijuana and placebo. The group means suggest that the peak "high" for the group is close to 30 minutes following smoking of marijuana, at which time it is 70 on the 0 to 100 scale. On the other hand, the peak "high" for the group after smoking placebo was about 24 and it occurred closer to 5 minutes post smoking.

	MARIJUANA					PLACEBO				
SUBJECT	Post 5 min	Post 30 min	Post 80 min	Post 120 min	Post 180 min	Post 5 min	Post 30 min	Post 80 min	Post 120 min	Post 180 min
003	88	85	25	5	0	40	60	0	0	0
004	93	98	57	40	15	0	0	0	0	0
005	80	76	71	8	6	0	0	0	0	0
007	85	85	50	20	5	15	0	0	0	0
008	50	60	70	60	45	35	50	60	50	--
010	50	80	40	35	18	5	0	0	0	0
011	80	85	85	85	65	20	15	20	10	0
014	60	70	70	70	--	25	20	--	0	0
015	55	60	45	40	35	15	15	--	10	5
021	40	70	20	13	4	35	14	--	--	0
022	80	80	50	50	--	50	30	13	0	0
023	30	--	40	30	25	45	40	8	0	0
024	50	30	30	10	0	50	50	20	15	--
025	60	83	85	65	30	0	0	0	0	0
026	50	40	25	15	--	20	5½	3	--	--
Mean	63.4	71.6	50.9	36.4	20.7	23.7	20.0	10.3	6.5	0.4
St.Dev.	19.4	18.7	21.6	25.2	20.2	18.1	21.0	17.5	14.1	1.4

Table XXIV: Subject's High Rating (0 to 100) after Smoking Marijuana (12 mg THC) or Placebo.

ALCOHOL

SUBJECT	Post 5 min	Post 30 min	Post 80 min	Post 120 min	Post 180 min	Second Drink	Post 5 min	Post 30 min	Post 80 min	Post 120 min
004	40/10	32/5	--	1/1	0/0					
014	50/50	50/65	60/60	30/30	10/10					
023	30/30	--	5/0	--	0/0					
012	--	25/	25/	--	--	Second Drink Post 30	25/	0/	--	0/
013	--	25/	20/	--	--	Second Drink Post 40	30/	20/	--	--

Table XXV: Subject's High Rating (0 to 100) after Drinking Alcohol (0.012 oz/lb). Ratings on Alcohol (Numerator) and Marijuana (Denominator) High Scales.

LIBRIUM

SUBJECT	Dose Given	Post 30-45 min	Post 60 min	Post 90 min	Post 120 min	Post 160-180 min	Post 390 min	2nd Dose	Post 30 min	Post 90 min
004	50 mg.	50/15	65/0	--	--	30/0	10/0			
014	25 mg.	7/5	0/5	--	0/0	--	--	2nd Dose (25 mg.) Post 160 Min	0/0	0/0
023	25 mg.	0/0	--	--	--	--	--	2nd Dose (25 mg.) Post 120 Min	--	0/0
014	25 mg.	15/0	--	--	--	--	--			

Table XXVI: Subject's High Rating (0 to 100) after Ingesting Librium (25 or 50 mg). Ratings on Alcohol (Numerator) and Marijuana (Denominator) High Scales.

The group data are presented graphically in Fig. 7 (lower curves). It is clear that the subjective "high" peaks later than the pulse rate (and presumably later than the peak plasma Δ^9 THC concentration) and is at 70% of its peak at a time when pulse rate is back to pre-smoking levels.

The subjective "high" experienced by placebo smokers is not a new finding. Many investigators have reported this result; the placebo reaction is a well established entity in marijuana research. Both naive and experienced users can get "high" on the placebo (Jones, 1971).

b. Alcohol

"High" estimates were solicited from 5 subjects following alcohol ingestion. The alcohol treatments were the same as those for the phoria task. The estimate of "high" was made in two ways. First, the subjects were asked to rate their "high" on a 0 to 100 scale where 0 was "not high at all" and 100 was the highest they had ever been after drinking alcohol. Second, subjects were asked to rate their "high" in terms of a 0 to 100 scale where 100 was the highest they had ever been after smoking marijuana. In effect, the subjects made "high" ratings on two different scales, an alcohol scale and a marijuana scale. The latter double rating was made on 3 subjects.

The results are shown in Table XXV. All subjects got "high" on the alcohol and attempted (somewhat reluctantly) to rate their high on a marijuana scale. The group is too small for formal group analysis and clear trends do not emerge.

c. Librium

Three subjects were given 50 mg of Librium, one in a single dose and two in divided doses. One subject was also given a subsequent dose of 25 mg some days later for a second experiment. The time schedule for the dosage and the individual "high" ratings are shown in Table XXVI. Since none of the subjects had taken Librium before, there could be no subjective "high" based on a Librium scale. Consequently, we asked the subjects to adopt both the alcohol scale and marijuana scale for their "high" estimate, giving a rating on each scale.

Generally, the subjects rated themselves fairly low on both scales. One subject (004), however, was more willing to assess his Librium "high" on his alcohol scale; he reached a maximum high approximately one hour after a 50 mg oral dose of Librium.

L. Subjective Drug Effects Questionnaire (S.D.E.Q.)

1. *Procedure*

Waskow *et al.* (1970) developed the S.D.E.Q. form which is designed to tap emotional, cognitive, and perceptual effects produced by psychoactive drugs by means of a 272 item symptom check list covering all aspects of subjective responses.

S.D.E.Q. forms were given to all subjects following marijuana, alcohol, Librium, and placebo treatments.

2. *Results*

An item analysis was performed to determine which questions discriminated between subjects showing an above-average intraocular pressure drop after smoking marijuana and those showing a below-average drop. The details of the item analysis and the relationship to the intraocular pressure measurements in marijuana, alcohol, and Librium experiments are discussed above in Specific Experiments, Section E.

IV. SUMMARY AND CONCLUSIONS

The major purpose of the present study was to employ objective and automated approaches to investigate vision functions that may be affected by socially relevant doses of marijuana. We were especially interested in establishing whether reported changes in glare recovery time and heterophoria could be verified by careful objective testing methods. Our previously developed glare recovery and heterophoria testing equipment was ideal for this purpose. Further, in accordance with our technical objectives, we explored other objectively measured vision functions as influenced by socially used drugs. The rationale for the inclusion of drugs other than marijuana (namely, alcohol and Librium) and for tests other than glare recovery and heterophoria is outlined in the Introduction of this Report.

Included in our experiments were measures of nine vision functions and five measures not specifically related to vision (reaction time, time estimation, pulse rate, "high" evaluation, and subjective drug effects). All vision functions were measured objectively. The results are presented under Specific Experiments and are summarized in Appendix A. Several of the more important results deserve special mention.

1. A widely publicized report (Frank *et al.*, 1971) of a several second increase in glare recovery time following marijuana smoking has been used to suggest that night driving might thereby become hazardous. Our objective and subjective measures of glare recovery for 14 subjects indicate a slight but statistically significant *decrease* in glare recovery time for the group after smoking marijuana. Objectively measured glare recovery times were reduced by about 7% for the group (namely, from 3.3 seconds pre-smoke to 3.1 seconds 30 minutes after smoking marijuana). Ten of our 14 subjects showed a decrease in glare recovery time. This finding is extremely important since recovery from glaring lights has both military and civilian significance. An increase in glare recovery time after smoking marijuana would be of concern to the military. However, our results suggest that marijuana smoking is unlikely to produce detrimental effects on visual recovery from blinding light flashes.

2. The pressure within the eye, intraocular pressure (IOP), was found to decrease within 5 minutes after smoking marijuana (12 mg THC) and to recover within 4 to 5 hours. IOP was at its minimum at about 80 minutes post-smoke where the drop amounted to about 2 mm Hg (statistically significant at the 0.02 level when compared to placebo). Only 7 of 15 subjects exhibited a clear decline in IOP after smoking marijuana. These subjects tended to be less-experienced marijuana users. The drug tended to produce in these subjects greater relaxation and tiredness, a greater "high" and a greater increase in pulse rate. Each of these four variables except pulse rate correlated significantly with IOP drop in the total sample. The observed decreases in IOP could have resulted from a direct effect of marijuana on ocular fluid dynamics. Part of the marijuana-induced IOP drop, however, may have been an epiphenomenon or secondary effect associated with the *subjective state* created by the drug. Such an indirect effect of marijuana mediated through relaxation and tiredness – a psychophysiological state that can be produced by drug and nondrug means – suggests that the search for means of controlling or preventing high intraocular pressure should include the possible role of relaxation.

3. Socially used drugs have been shown to affect certain aspects of visuomotor control (Moses, 1970). We examined several visuomotor functions: tonic eye posture (heterophoria), saccadic eye movements, smooth pursuit eye movements, and reflex optokinetic nystagmus. The results suggest subtle changes in each of these functions, some of which need further exploration. A statistically significant change in smooth pursuit eye movements occurred with alcohol intoxication (mean performance 2.2 Hertz before alcohol and 1.8 Hertz after alcohol). Following marijuana smoking, there was no evidence of a decrease in pursuit eye movement performance. The integrity of eye movements is important in many civilian and military tasks involving search and tracking; the degree to which marijuana, alcohol, and other socially used drugs can contribute to decrements in eye movement performance needs to be determined. Future studies should be directed toward clarifying the differences between alcohol and marijuana, examining dose relationships, increasing the task complexity, and demanding divided attention in the task.

4. Pulse rate invariably increased after marijuana smoking: this result confirms most previous studies where pulse was measured. Pulse rate has recently been reported to be a correlate of blood plasma THC concentration; it would, therefore, appear practical to follow pulse rate during experiments performed after giving marijuana and to use pulse rate increase as an indirect measure of THC intake. To our knowledge the time course of pulse rate has not been carefully studied. The pulse rate is generally believed to peak between 10 and 20 minutes following marijuana smoking. Continuous pulse monitoring in our experiments revealed that the pulse rate starts to rise within a few minutes after beginning to smoke marijuana, and reaches a maximum within 5 minutes after the smoking stops. This result has not been reported before; it suggests a very rapid absorption of Δ^9THC with prompt physiological effects.

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APPENDIX A

SUMMARY OF EXPERIMENTAL RESULTS

MARIJUANA (12 mg THC), ALCOHOL (.012 oz/lb), LIBRIUM (50 mg)

FUNCTION	RESULTS	COMMENTS
A. GLARE RECOVERY	Marijuana (n=14) Slight, statistically significant reduction in glare recovery time, both subjectively and objectively (Approximately 7%).	• Suggests possible difference between marijuana and alcohol. Need to use higher dosage of marijuana and more subjects with alcohol. • Need to explore glare recovery to different performance levels where there may be a more marked effect by marijuana.
	Alcohol (n=3) Slight increase in glare recovery time both subjectively and objectively.	
	Librium (n=3) Slight increase in glare recovery time both subjectively and objectively.	
B. [illegible]ORIA	Marijuana (n=14) No significant change in heterophoria for group data. Individual subjects have shifts in phoria (both esophoric and exophoric).	• High doses of marijuana may reveal changes. Should be pursued in future studies with check on influence of proximal convergence.
	Alcohol (n=5) 3 subjects show esophoric shift. Two subjects show exophoric shift.	• Need more subjects on alcohol to see trend.
	Librium (n=3) All 3 subjects show exophoric shift at 50 mg dose (Approximately 15% mean shift).	• Librium experiments should be pursued on more subjects at different doses.

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FUNCTION	RESULTS	COMMENTS
C. OKN	Marijuana (n=14) Reduction in amplitude, frequency, and regularity of OKN in many subjects.	●Further analysis and experiments may help to differentiate effects of alcohol and marijuana on these eye movements.
D. REACTION TIME	Marijuana (n=5) No change in simple reaction time.	●Reaction time is useful in checking for influence on subjective response to tests such as glare recovery.
	Alcohol (n=5) Slight increase in reaction time in 2 of the 3 subjects. Not significant in group data.	●Result is consistent with the literature on simple reaction time.
	Librium (n=3) No significant change in group data.	●Results with alcohol and Librium need to be done on a larger group before conclusions and comparisons made with marijuana.
E. INTRAOCULAR PRESSURE (IOP)	Marijuana (N=15) About 15% drop in IOP in group data. Statistical significance 80 minutes after smoking. Individual differences marked. Placebo shows corresponding 5% drop. For two subjects who showed drops at 12 mg dosage, 22 mg THC produced significant drop in IOP. Alcohol (n=3) Subjects who show IOP drop with 12 mg THC show IOP drop with alcohol. Subject with questionable change in IOP with 12 mg THC shows change in IOP with alcohol.	●At socially relevant dosage the mean drop in IOP is only significant for the group 80 minutes after smoking. ●Those subjects who show IOP drop may show a similar drop with other "relaxing" drugs such as alcohol and Librium. Subject questionnaire suggests correlation between IOP drop and pleasant tiredness. ●Should be studied at higher doses of marijuana and with other drugs at different dosages. ●Relaxation index should be determined for each subject in each experiment.
IOP (con't)	Librium (n=3) All 3 subjects show drop in IOP with 50 mg Librium. The one subject on a second lower dosage (25 mg) did not show IOP drop.	
F. SACCADIC EYE MOVEMENTS	Marijuana (n=13) Saccadic eye movement rhythm is faster after smoking marijuana. Alcohol (n=3) Two subjects faster and one slower rhythm. Librium (n=3) All 3 subjects show faster rhythm.	●Short term memory required to make predictive saccadic eye movements is altered by marijuana at 12 mg dosages. ●Evidence that internal clock changes are revealed by saccadic eye movement rhythm after smoking marijuana. ●Some subjects showed increased difficulty in following the light stimulus following marijuana intoxication. ●The results suggest that a more complex saccadic eye movement stimulus in a divided attention task should be pursued.
G. TIME ESTIMATION AND TIME PRODUCTION	Marijuana (n=14) Time production decreased and time estimation increased. (The reverse is true for the placebo condition!) Alcohol (n=3) On 3 subjects; two showed increased time production and one showed decreased time production. Librium (n=3) On 3 subjects; two showed increased time production and one showed decreased time production. One subject showed increased time production and decreased time estimation at both the 25 mg and 50 mg doses.	●Results are consistent with a "speeding up" of the internal clock after smoking marijuana. Time production may be the most valid measure of changes in the internal clock. Should be pursued with any vision tests which involve subjective time judgments, e.g., prolongation of after images. ●May be a real difference between marijuana and alcohol. Time production should be studied further with alcohol and Librium at different doses and more subjects. Potential index of drug interaction effects.

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FUNCTION	RESULTS	COMMENTS
J. PULSE RATE	Marijuana (n=15) Group data shows a large increase (approx. 40%) in pulse rate peaking close to 5 minutes after smoking. The placebo produced a slight increase in pulse rate (less than 5%) peaking close to 5 minutes after smoking. Individual subjects show that the peak pulse rate occurs less than 5 minutes after smoking marijuana. Alcohol (n=5) No change in pulse rate. Librium (n=3) No change in pulse rate.	• This is a most consistent and marked change measured with marijuana smoking. • Should be measured with all future vision function in drug studies because: • (1) it reflects Δ^9THC content, and (2) it represents a monitor of cardio-vascular condition of the subject.
K. HIGH RATING	Marijuana (n=15) Mean high rating 72 (on 0-100 scale) peaking at 30 minutes after smoking marijuana. Placebo produced mean high rating of 24, peaking close to 5 minutes after smoking.	• Significant "high" ratings produced with marijuana and placebo. Time course of "high" different for the marijuana, being longer and peaking later than for the placebo. • "High" ratings followed significantly slower time course than the pulse rates.
L. S.D.E.Q.	Marijuana (n=15) Certain relaxation items significantly correlated with IOP drop. Alcohol (n=5) Relaxation scale not correlated with IOP drop. Librium Relaxation scale possibly correlated with IOP drop.	• S.D.E.Q. forms enable hypothesis testing of subjective effects relation to performance or physiology change. • IOP drop significantly correlated to patients' reports of peaceful relaxation and tiredness.

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FUNCTION	RESULTS	COMMENTS
H. SINUSOIDAL PURSUIT EYE MOVEMENTS	Marijuana (n=14) No significant reduction in smooth sinusoidal tracking.	• Results suggest qualitative changes in eye movement tracking performance. Should be continued in divided-attention experiment, at both upper and lower velocities.
	Alcohol (n=5) Results indicate reduced performance at high velocities.	• Should be studied in more subjects at 3 dose levels.
	Librium (n=3) Complex background condition produced reduction in tracking performance in all 3 subjects. Simple condition - no change.	• Suggests possible differences in marijuana and alcohol. Should be pursued in divided-attention task.
I. (a) PUPIL SIZE	Marijuana (n=9) Results suggest slight constriction of pupil diameter (less than 0.4 mm).	• Slight constriction contrary to popular belief that marijuana produces dilation of the pupil.
	Alcohol (n=3)	• Not profitable to pursue further in view of very small changes found.
(b) CONJUNCTIVAL INJECTION	Marijuana (n=15) Results show consistent conjunctival injection.	• Consistent with many other marijuana studies. Not profitable to pursue further.
(c) LID EDEMA - PTOSIS	Marijuana (n=15) Results suggest edema of lids and slight ptosis.	• Ptosis and edema probably related.